United States Court of Appeals for the Second Circuit



APPELLANT'S APPENDIX

75-7143



In The

MITTED STATES COURT OF APPEALS

For The Second Circuit

No. 75-7143



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MALACHY J. SMYTH and LUCY SMYTH,

Plaintiffs-Appellants,

vs.

THE UPJOHN COMPANY,

Defendant-Appellee.

On Appeal from the United States District Court

For the Northern District of New York

APPELLANIS' APPENDIX

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UNITED STATES DISTRICT COURT NORTHERN DISTRICT OF NEW YORK

MALACHY J. SMYTH and LUCY SMYTH,

Plaintiffs,

v. : Civil No. 71-CV-412

THE UPJOHN COMPANY,

Defendant.

The following is portion of the proceedings held on the 22nd day of January, 1975, at the United States District Court, Utica, New York, before HONORABLE EDMUND PORT, United States District Judge, and a Jury.

APPEARANCES:

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(The following is a portion of the direct examination of Dr. Robert B. Wallace.)

BY MR. COUPE:

Q Doctor, I show you supplement C of 1970 to the same Physicians Reference, and ask you to read the warning section.

MR. HUNT: Excuse me. Is that marked?

MR. COUPE: That is marked.

MR. HUNT: I object, Your Honor, that was not received in evidence.

MR. COUPE: Very well, I will offer it in evidence.

MR. HUNT: I would object to it as irrelevant.

THE COURT: Didn't I pass on that?

MR. HUNT: You did, Your Honor.

THE COURT: May I see it?

MR. HUNT: At the time you said there was not sufficient foundation.

THE COURT: All right. What is the purpose of it? Do you want me to withdraw the jury?

MR. HUNT: I would think so.

THE COURT: Step up to the bench.

(The following proceedings took place at the bench outside the hearing of the jury.)

MR. COUPE: I have briefed the question because of the Incollingo case, the Pennsylvania —

THE COURT: Now the Incollingo case, the purpose of this was to show the relative ease with which it could be amended, but you are not offering it for that purpose and I don't even know that is a question here, and the trouble with the Incollingo case is that from the case itself there is no way to determine what the facts are, except there is a conditional warning given at a later date, and the court said that it was such a simple matter.

Now, I don't know, for instance, it could have been the situation where it was sufficiently serious as to require telephone calls, as to require situations that arise where there was a sudden epidemic that could require calling up these people, taking the stuff off the shelf—taking it off the shelves immediately and sending telegrams to the doctors to stop prescribing it, recall all your prescriptions, broadcasting to the pharmacies not to fill prescriptions. I don't see any such thing here. The only thing I see here is an effort — you have to balance the prejudice that is going to be created against the defendant and weigh it on those scales. I can't see the worth of it.

MR. COUPE: Not weighed on that scale, not on those scales.

THE COURT: The fact that you start with the premise that -- the statements later are inadmissible as a matter of public policy. Now if there is something that outweighs that public policy --

MR. COUPE: Could I argue this formally? I would like to make a record on it. It would be fairly lengthy.

THE COURT: I am afraid you are prejudiced on a verdict if you get one.

MR. COUPE: I don't want to make an argument in from of the jury,
I want to make an argument outside of the jury.

THE COURT: You want to be longer?

MR. COUPE: Yes.

THE COURT: All right.

The jury may step down.

(The jury was excused and the following proceedings took place outside the presence of the jury.)

MR. COUPE: Your Honor, at this time I would urge that you admit into evidence subsequent articles of the Physician's Desk Reference which show an increase in the warnings in the — between the years 1970 and 1974.

The Court in Incollingo against Ewing, the Pennsylvania case which Your Honor has been referred to, states that although precautions taken after the acts complained of are inadmissible for the purpose of proving antecedent negligence, such evidence is admissible if competent for any purpose as long as it is so qualified by instructions to the jury.

Now among the cases which I have cited are a case in the New York Court of Appeals, Miller versus the Ocean Steamship Company of Savannah, 118 New York, 199 in which the Court of Appeals held that where the plaintiff's injury was caused by the breaking of a stick used to hold a pulley block through which a hawser passed, it was proper to permit the plaintiff to prove over objection that immediately after the accident the place of the stick was effectually supplied by one of the capstan bars which were near in order to successfully complete the operation first intended.

Also in this state it has been said that a well known exception to the general rule is that evidence of remedial action is admissible to show that it was possible and practical to have avoided the accident, although the court must instruct the jury that remedial action is not to be considered an act of negligence, and I refer Your Honor to 17 ALR 61, and 64 ALR (2d) 1315.

And again this doctrine has not been closely followed in modern times, it is an old doctrine and the courts have sought exceptions to its application.

Now, as Your Honor pointed out, the reasons that were given in the old cases were that to allow such proof to be given would be against public policy, and I should like to point out to Your Honor that there is one well known exception, and that is where it is used to prove that the defendant had control of the instrumentality which caused the negligence.

THE COURT: I am familiar with that. We don't have any question of control.

MR. COUPE: But if that were so, if public policy were to be supreme, even that exception would not be allowed.

Now let me point out to Your Honor further that the FDA regulation under Title 21 of the United States Code, and that is Section 1.106, requires full disclosure by drug companies to dispensing physicians so that the physician may protect any person who consults him against an adverse reaction.

The Section states that labeling on or within the package from which the drug is to be dispensed must bear adequate information for its use, including indications, effects, dosages, routes, methods and frequency and duration of administration, and, I emphasize, and any relevant hazards, contraindications, side effects and precautions under which practioners licensed by law to administer the drug can use the drug safely, and for the purposes for which it is intended, including all purposes for which it is advertised or represented.

The leading textbook in this field written by -

THE COURT: Do you have a case that — I have been unable to find one, I am not acquainted with a case that affords a civil action by reason of the violation of the Food and Drug Act.

MR. COUPE: I have not been able to find one.

THE COURT: Well, then, the Mer 29 case, the Court specifically eliminated that question from consideration.

MR. COUPE: I think that the Court has to interpret the regulation, and I believe that this regulation makes it incumbent upon the drug companies to report everything which they know about a drug to the FDA, and I think that the purpose of the entire statute is to have the medical profession sufficiently warmed.

Now my offer of proof is this, based upon the adverse reactions which Dr. Wallace has examined, that in his opinion the warning which existed in 1970 following the taking of the drug by Dr. Smyth was insufficient, because it merely mentioned an acute colitis; that the warning which was mentioned in 1972 and which is in large blocks —

THE COURT: Well, let's get the record straight. You have offered Exhibit 11A, what is that?

MR. COUPE: 11A is a supplement, 1970 --

THE COURT: 1970?

MR. COUPE: Yes.

THE COURT: Well, isn't that the same as your textbook?

MR. COUPE: No.

THE COURT: In what respect is it different?

MR. COUPE: It differs in that after the words "Associated with blood and mucus ir ..e stools" appear the following: "And has at times resulted in an acute colitis."

THE COURT: The word "acute" is the only difference, is that right?

MR. COUPE: No, "colitis" has never been mentioned before.

THE COURT: And this book came out when?

MR. COUPE: This came out sometime in 1970, following Dr. Smyth's taking of the drug.

MR. HUNT: Excuse me, what are you referring to now?

MR. COUPE: The supplement of 1970.

THE COURT: All right.

MR. COUPE: Now my point is this. Mr. Hunt has made a great to do about the words "enterocolitis" and from the year 1970 until today the adverse reaction section reads the same, it is "gastrointestinal, glossitis, stomatitis, nausea, vomiting, persistent diarrhea, enteroblitis and pruritis ani." This is the same thing in the adverse reaction section except that in —

THE COURT: The 1970 adverse reaction, I think, is more condensed, isn't it, stomatitis, nausea, persistent diarrhea, enterocolitis and pruritis ani?

MR. COUPE: Those are the same. Every year it is the same, so my argument is this, and it has been demonstrated to be a valid argument from the cases, that they have watered down that portion of the PDR so that it is meaningless, and the one which they concentrate on is the warning section.

Now the warning section has been changed over the years so that we have a warning section in 1972 where there are heavy block letters, that is at page 1459 of the 1972 PDR.

THE COURT: So what are you proposing using this evidence for?

MR. COUPE: I will have Dr. Wallace testify that in his opinion the warning which existed in 1970 was insufficient.

THE COURT: All right, great, that puts you in good position.

MR. COUPE: He will testify that --

THE COURT: I am talking about this supplement, what use is this supplement to you?

MR. COUPE: To show that they should have used that warning. Really they should have used the warning they had in 1974.

THE COURT: Well, -

MP. COUPE: Based upon what he has examined.

THE COURT: That is actually exactly what I am getting at, isn't that precisely what you can't use it for?

MR. COUPE: If he states that in is opinion --

THE COURT: But isn't that precisely what you just got through telling me, that you can't use subsequent repairs or subsequent events to establish negligence?

MR. COUPE: You can use it as an exception to that rule.

THE COURT: For what purpose?

MR. COUPE: For a foundation.

THE COURT: For instance, in your Pennsylvania case they used it for one purpose, to show the simplicity with which it could be changed, perhaps a telephone call to get it out to the trade. In the after repair cases, as you have indicated, it is used where control is denied, it must be established, but it isn't used to establish negligence.

All right, I will hear from Mr. Hunt so you can make a record.

MR. HUNT: I believe I have briefed the point.

THE COURT: Well, you briefed it, the court has made an argument for you.

MR. HUNT: Just as I said at the bench, this evidence carries with it a potential for prejudice which should not be in the case. It is apparent from counsel's statement that that is the use to which the evidence would be put.

The adverse reactions are the same, the warnings, true, have added "acute" colitis. If on the basis of the adverse reports acute colitis should have been contained in the warning prior to the time that the plaintiff administered the drug to himself, that can be argued to the jury, but weighing the prejudice against the legitimate value of this evidence, I find it wanting.

THE COURT: The objection is sustained. All right, you have got a complete record.

MR. COUPE: All right. Now, Your Honor, --

THE COURT: Now let's get on with the trial.

MR. COUPE: May I ask this, Your Honor? Would Your Honor permit me to inquire of the doctor what in his opinion would be sufficient warning?

THE COURT: It probably requires a very liberal view of the evidence, but I will let you ask it.

MR. COUPE: All right.

MR. HUNT: Well, Your Honor, I would hope that the doctor would not answer what was subsequently put in, because I would move for the withdrawal of a juror.

THE COURT: What do you mean, what was subsequently put in?

MR. COUPE: He means the PDR's.

MR. HUNT: In other words, I would hope the doctor wouldn't answer what they put in in their later insert.

MR. COUPE: Well, you have ruled, Your Honor.

THE COURT: Let me see, you are going to ask the doctor —
after all, are we concerned with what the doctor thinks would be
good? We are only concerned with what — we have let him say that that
is what has been done was poor practice — now it doesn't make any
difference what he thinks is good, does it?

MR. COUPE: Yes, it does.

THE COURT: It doesn't to me. I am going to reverse myself.

Supposing he thinks it should be decked out in red, white and blue,
who cares?

MR. COUPE: The medical profession.

THE COURT: Yes, but it is the jury that is going to decide that.

MR. COUPE: But he has to express an opinion to the jury.

THE COURT: No, I won't permit it. I have let it go as far as I will, you have made an offer of proof and I have ruled.

MR. COUPE: Your Honor, may I have one more word?

THE COURT: Yes. You are running out of words, I will tell you that.

MR. COUPE: All right, Your Honor, in no way will he refer -

THE COURT: No, I don't want to try this case over again, we have gotten too deeply into it.

MR. COUPE: All right, I will take an exception to Your Honor's ruling.

This is to certify that the foregoing record is a true and accurate transcript of a portion of the proceedings had at the time and place noted in the heading her.

/s/ Martin L. Miller

MARTIN L. MILLER Official Reporter United States District Court Northern District of New York . roduct Information

against most of the common gram-positive pathogens. Depending on the sensitivity of the organism and concentration of the antibiotic, it may be either bactericidal or bacteriostatic. It has not shown cross resistance with other available antibiotics. Microorganisms have not developed resistance to Lincoln rapidly when tosted by in ance to Lincocin rapidly when tested by in

witro or in vivo methods.
Studies indicate that Lincocin does not share antigenicity with penicillin compounds. During the clinical investigation of pounds. During the clinical investigation of Lincocin, the drug was given to over 460 persons with known allergies (including persons reported to be allergic to penicilin). No serious hypersensitivity reactions were reported in these patients. In subsequent clinical experience many patients have received repeated courses of Lincocin (lincomycin hydrochloride memohydrate) without developing evidence of hypersensitivity. However, a few cases of hypersensitivity reactions have been reported, some of these in patients known to be sensitive to penicillin. (See Precautions and Adverse Reactions Sections.)

Actions:

Actions: Biological Studies—In vitro studies indicate that the spectrum of activity includes Micrococcus (Staphylococcus) aureus, Staphylococcus albus, β-hemolytic Streptococcus, Streptococcus viridans, Diplococcus pneumonine, Clostridium tetani, Clostridium perfringens, Corynebacterium diphtheriae and Corynebacterium acnes.

The drug is not active against most strains The drug is not active against most strains of Streptococcus faecalis, nor against Neisseria gonorrhoeae, Hemophilus influenzae (with the 2y disk), or other gram-

fluenzac (with the 2γ disk), or other gram-negative organisms or yeasts.

In vivo experimental animal studies demonstrated Lineocin's effectiveness in protecting animals infected with Strep-tococcus viridans, β-hemolytic Streptococ-cus, Micrococcus aureus, Diplococcus pneumoniae and Leptospira pomona. It was ineffective in Klebsiella, Pasteurella, Pseudomonas, Salmonella and Shinella in-Pseudomonas, Salmonella and Shigella in-

fections. Cross resistance has not been demonstrated with penicillin, erythromycin, triacetylo-leandomycin, chloramphenicol, novobio-cin, streptomycin or the tetracyclines. Staphylococci develop resistance to Lincocin in a slow, step-wise manner based on in vitro, serial subculture experiments. This pattern of resistance development is unlike that shown for streptomycin.

Clinical Absorption and Excretion-Lincocin is absorbed rapidly after a 500 mg, oral dose, reaching peak levels in 2 to 4 hours. Levels are maintained above the MIC (minimum inhibitory concentration) for most gram-positive organisms for 6 to 8 hours. Urinary positive organisms for the following period ranges from 1.0 to 31 percent (mean: 4.0) after a single oral dose of 500 mg. Tissue level studies indicate that bile is an imporlevel studies indicate that the is an impor-tant route of exerction. Significant levels have been demonstrated in the majority of body tissues. Although the drug is not pre-sent in significant amounts in the spinal fluid of normal volunteers, it has been demonstrated in the spinal fluid of one pa-tient with progressed magingitis.

demonstrated in the spinar fund of the partient with pneumococcal meningitis.

Intramuscular administration of a single dose of 600 mg, produces a peak serum level at 30 minutes with detectable levels persisting for 24 hours. Urinary excretion after this dose ranges from 1.8 to 24.8 percent (mean: 17.3)

The intravenous infusion over a 2-hour interval of 600 mg. of Lincocin (lincomycin hydrochloride monohydrate) in 500 ml. of b percent glucose in distilled water yields therapeutic levels for 14 hours. Urinary excretion ranges from 4.9 to 30.3 percent (mean: 13.8).

The biological half-life, after oral, intramuscular or intravenous administration is 5.4 ± 1.0 hours.

Indications: Lincocin (lincomycin hydrochloride monohydrate) is indicated in in-fections caused by gram-positive organ-

isms which are susceptible to its action, particularly streptococci, pneumococci and staphylococci. As with all antibiotics, in vitro susceptibility studies should be per-

Lincocin has 'een demonstrated to be effective in the treatment of staphylococcal infections resistant to other antibiotics and susceptible to lincomyein. Staphylococcal strains resistant to Lincocin have been recovered; culture and susceptibility stud-

recovered; culture and susceptibility studies should be done in conjunction with Lincocin therapy. The drug may be administered in combination therapy with other antimicrobial agents when indicated. Contraindications: As with all drugs, the use of Lincocin is contraindicated in patients previously found to be hypersensitive to the drug. It is not indicated in the treatment of minor bacterial infections or treatment of minor bacterial infections or viral infections.

Until further clinical experience is obtained, Lincocin is not indicated in the

Warning: Cases of severe and persistent diarrhea, some with blood and mucus in the stools have been reported and at times have necessitated discontinuance of the drug. This side effect usually has been associated with the oral dosage form but has occa-sionally been reported following parenteral

therapy. Precautions: Lincocin, Precautions: Lincocin, like any drug, should be used with caution in patients with a history of asthma or significant al-

The use of antibiotics occasionally results in overgrowth of nonsusceptible organisms in overgrowth of nonsusceptible organisms—particularly yeasts. Should superin/ections occur, appropriate measures should be taken. When patients with pre-exa, ing monitial infections require Lincoein therapy, concomitant antimonilial treat-

ment should be given.

During prolonged Lincocin (lincomycin hydrochloride monohydrate) therapy, periodic liver function studies and blood

counts should be performed.
Safety for use in pregnancy has not been established. Experience with 345 women receiving the drug during various stares of pregnancy revealed no ill effects in the mother or fetus.

Since adequate data are not yet available in patients with pre-existing liver disease, its use in such patients is not recommended at this time unless special clinical circumstances so indicate. Efficacy of Lincocin in the prophylactic treatment of rheumatic fever has not been established.

Adverse Reactions:

Jastrointestinal-Glossitis, stomatitis, nau-

sea, vomiting, persistent diarrhea, enterocolitis and pruritis ani.
Hemopoietic—Neutropenia, leukopenia and thrombocytopenic purpura have been reported. No irreversible hematologic toxicis has been reported.

icity has been reported.

Hypersensitivity Reactions—A few cases of hypersensitivity reactions such as angioneurotic edema, serum sickness and anaphylaxis have been reported. If an allergic reaction should occur, the drug should be discontinued and the usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment. city has been reported. treatment.

Skin and Mucous membranes-Skin rashes, urticaria and vaginitis. A rare case of ex-foliative dermatitis has been reported.

Liver-Although no direct relationship of Lincocin to liver dysfunction has been established, abnormal liver function tests

Continued on next page

Information on these Upjohn products is based Information on these Upjohn products is based on labelling in effect on July 1, 1969. Further information on dosage and administration, side effects, precautions and contraindications for these and other Upjohn products may be obtained from either the package brochure or Medical Services, The Upjohn Company, Kalamazoo, Michigan.

LINCOCINO (lincomycin hydrochloride monohydrate,

Upjolin) Lincomycin, a new antibiotic produced by Streptomyces lincolnesis var. lincolnesis, is chemically distinct from all other clinically chemically distinct from all other clinically available antibiotics and is isolated as a white crystalline solid. It is stable in the dry state and in aqueous solution for at least 24 months. Lincomycin is readily soluble in water at room temperature in concentrations up to 500 mg./ml. Physical stability of aqueous solutions can be maintnined at drug concentrations up to 345 mg./ml. at temperatures as low as 4° C. Lincocin has been shown to be effective

Product Information

Always consult Supplement

Upjohn-Cont.

particularly elevations of serum transamihave been observed in a few in-

o serious renal or neurologic abnormali-

ties have been reported.

No ototoxicity has been demonstrated in any of a large number of patients treated with Lincocin.

Local Reactions-Patients have strated excellent local tolerance to in-tramuscularly administered Lincocin. Reports of pain following infection have been

infrequent. Intravenous administration of Lincocin (lincomycin hydrochloride monohydrate) in 250 to 500 ml, of 5 per cent glucose in distilled water or normal saline produced no local irritation, phlebitis or systemic side effects.

Dosage and Administration: Oral-Adults: Mild to moderately severe infections-500 mg. 3 times per day (500 mg. approximately every 8 hours). Severe infections-500 mg. or more 4 times per day (500 mg, or more approximately every 6

Children over I month of age: Mild to modcontacts over 1 month of age; what to moderately severe infections—30 mg./Kg./day (15 mg./ib./day) divided into 3 or 4 equal doses. Severe infections—60 mg./kg./day (30 mg./lb./day) divided into 3 or

4 equal doses. For optimal absorption it is recommended that nothing be given by mouth except wathat nothing be given by mouth except water for a period of one to two hours before and after oral administration of Lincocin. Intramuscular—Adults: Mild to moderately severe infections—600 mg. (2 cc.) intramuscularly every 24 hours. Severe infections—600 mg. (2 cc.) intramuscularly every 12 hours or more often. Children over, 1 month of age: Mild to moderately every infections—one intramuscular infec covere infections—one intramuscular injec-ion of 10 mg./kg. (5 mg./lb.) every 24

ion of 10 mg./kg. (5 mg./lb.) every 24 urs. Nevere infections—one intramuscut injection of 10 mg./kg. (5 mg./lb.) every 12 hours or more often. intravenous—Adults: 600 mg. (2 cc.) intravenously every 8 to 12 hours. For intravenous administration, Lincocin should be added to 250 cc. or more of 5 per cent glucose in water or normal saline and given as an infusion.

Children over 1 month of age: 10 to 20 mg./kg./day (5 to 10 mg./lb./day) divided into 2 or 3 doses and given as an infusion at 3 to 12 hour intervals. The method of administration is the same as noted above for

adults. For more serious infections, these doses may have to be increased. With \$\beta\$- hemolytic streptococcal infections, treatment should continue for at least 10 days to diminish the likelihood of subsequent rheumatic fever or glomerulonephritis. Patients with diminished renal function: When Lincocin therapy is required in individuals with severe impairment of renal function, an appropriate dose is 25 to 30% of that recommended for patients with normally functioning kidneys.

How Supplied:

Capsules

250 mg. (Pediatric), each capsule contains lincomycin hydrochloride mono-hydrate equivalent to 250 mg. lincomycin in bottles of 24 and 100, 500 mg., each capsule contains lincomy-

cin hydrochloride monohydrate equivalent to 500 mg. lincomycin in bottles of 24 and 100. Unit-Dose Package Foil Strip of 100 capsules. Sterile Solution, each cc. contains lincomy-

cin hydrochloride monohydrate equiva-lent to 300 mg. lincomycin, also benzyl alcohol 9 mg., water for injection q.s. in 2 cc. and 10 cc. vials, and 2 cc. disposable

rup, each cc. contains lincomycin hy drochloride monohydrate equivalent to

50 mg. lincomycin, preserved with methylparaben 0.075%, propylparaben 0.025%, and sorbic acid 0.1%, Raspberry flavored; in 60 cc. and pint bottles.

Drops, each cc. contains lincomycin hydro-chloride monohydrate equivalent to 50 mg. lincomycin; preserved with methyl-paraben 0.075%, propylparaben 0.025%, and sorbic acid 0.1%. Raspberry fla-vored; in 30 cc. bottles.

Shown in Product Identification Section] Capsules, 500 mg.

Military Stock # FSN 6505-926-4769

Military Stock # FSN 6505-912-2404 VA Stock # SN 6505-912-2404A Sterile Solution, 300 mg./cc., 10 cc.: Military Stock # FSN 6505-926-4768

VA Stock # SN 6505-943-4374A.

MOICES III OULUES OF TOO.

LINCOCIN®

(lincomycin hydrochloride monohydrate, Upjohn)

Upjohn)
Prescribing information for this product, which appears on pages 1385-1386 of the 1970 PDR, has been revised and is completely replaced by the following. Please write "See Supplement C" alongside product heading in the 1970 PDR.

Description: Lincomycin, discovered and developed by The Upjohn Company, is an anti-biotic produced by Streptomyces lincolnensis var. incolnensis. Chemically it is 6,8-dideoxy-6-trans-(1-methyl-4-propyl-L-2-pyrrolidinecar-boxamido)-1-thio-D-crythro-n-D-galactoocto-pyranosside.

Actions:

Actions:
Microbiology—Lincocin has been shown to be effective against most of the common gram-positive pathogens. Depending on the sensitivity of the organism and concentration of the antibiotic, it may be either bactericidal or bacteriostatic. Cross resistance has not been demonstrated with penicilin, chloram-

phenicol, ampicilin, cephalosporins or the tetracyclines. Despite chemical differences, inconycin exhibits antibacterial activity similar but not identical to the macrolide antibiotics (e.g. crythromycin). Some cross resistance (with crythromycin) including a phenomenon known as dissociated cross resistance or macrolide effect has been reported. Microorganisms have not developed ported. Microorganisms have not developed resistance to Lincocin rapidly when tested by in vitro or in vivo methods. Staphylococci develop resistance to Lincocin in a slow, step-wise manner based on in vitro, serial subculture experiments. This pattern of resistance development is unlike that shown

for streptomycin, Sindies indicate that Lincocin (lincomycin hydrochloride mono hydrate) does not share antigementy with penicitin compounds.

amigenicity with penicinn compounds. Eliological Studies—In vitto studies indicate that the spectrum of activity includes Micrococcus (Staphylococcus) aureus, Staphylococcus albus, B-hemolytic Streptococcus, Streptococcus viridans, Diplococcus pneumoniae, Clostridium tetani, Clostridium pertringens, Cornebacterium diphtheriae and Cornebacterium acnes. fringens, Corynebacteri Corynebacterium acnes.

NOTE: The drag is not active against most strains of Streptococcus faccalis, nor against Neisseria gonorrhoeae, Hemophilus influor other gram-negative organisms or

Homen Pharmacology-Lincocin is absorbed rapidly after a 500 mg, oral dose, reaching peak levels in 2 to 4 hours. Levels are maintained above the MIC (minimum inhibitory tained above the MIC (minimum inhibitory educentration) for most gram-positive organisms for 6 to 8 hours. Urinary recovery of origin a 24-hour period ranges from 1.0 to 34 percent (meant 4.0) after a simple oral dose of 500 mg. Tissue level studies indicate that bile is an important route of exerction. Significant levels have been demonstrated in the majority of body tissues. Although the demonstrated in the majority of body tissues. though the drug is not present in significant amounts in the spinal fluid of normal volun-teers, it has been demonstrated in the spinal feers, it has been demonstrated in the spinal

Intramuscular administration of a single dose of 600 mg, produces a peak serum level at 30 minutes with detectable levels persisting for 24 hours. Urlinary excretion after this dose ranges from 1.8 to 24.8 percent (mean:

The intravenous infusion over a 2-hour interval of 600 mg, of Lincocin (lincomy hydrochloride monohydrate) in 500 ml, o percent glucose in distilled water yields therapeutic levels for 14 hours. Urinary ex-cretion ranges from 4.9 to 30.3 percent (mean: 13.8).

The biological half-life, after oral, intra-muscular or intravenous administration is 5.4 ± 1.0 hours.

indications: Lincocin is indicated in infections due to susceptible strait, of strepto-cocci, pneumococci and staphylococci. As with all antibotics, in vitro susceptibility studies should be performed.

Lincocin has been demonstrated to be effective in the treatment of staphylococcal infec-tions, resistant to other antibiotics and sus-ceptible to fincomycin. Staphylococcal strains ceptible to lincomycin. Staphylococcai strains resistant to 1 incocin have been recovered; culture and susceptibility studies should be done in conjunction with Lincocin therapy. In the case of macrolides, partial but not complete cross resistance may occar (see "Microbiology"). The drug may be administred conconstantly with other antimicrobial agents when indicated.

Contraindications: As with all drugs, the use of a incocin is contraindicated in patients previously found to be hypersensitive to the drug. It is not indicated in the treatment of minor bacterial infections or viral infections Warnings: Cases of severe and persistent diarrhea have been reported and have at times necessitated discontinuance of the drug. This diarrhea has been occasionally associated with blood and mucus in the stools and has at times resulted in an acute collis. This side effect usually has been associated

the oral dosage form but occasionally has the oral dosage form our occasionary man-been reported following parenteral therapy. Although no cross sensitivity with other anti-botic agents has been demonstrated, a care-ful inquiry should be made concerning pre-vious sensitivities to drugs and other al-

Usage in Pregnancy-Safety for use in pregnancy has not been established.

Usage in Newborn-Unut further clinical

xperience is obtained, Lincocin is not in-licated in the newborn.

Prevantions: Lincocin (lincomycin hydro-chloride monohydrate), like any drug, should be used with caution in patients with a his-tory of astlinia or significant allergies.

tory of astima or significant altergies. The use of antibiotics occasionally results in overgrowth of nonsusceptible organisms—particularly yeasts. Should superinfections occur, appropriate measures should be taken. When patients with pre-existing monibal infections require Lincocin therapy, concomitant antimonibal treatment should be given. e given.

During prolonged Lincocia therapy, periodic liver function studies and blood counts should be performed. Since adequate data are not yet available in

patients with pre-existing liver disease, its use in such patients is not recommended at this time unless special clinical circumstances

Adverse Reactions:

Gastrointestinal-Glossitis, stomatitis, sea, vomiting. Persistent diarrhea, enterocoli-tis and pruritus ani. (See "Warnings").

Hemopoletic-Neutropenia, leukopenia, agranulocytosis and thrombocytopenic purpura have been reported.

Hypersensitivity Reactions-Hypersensitivity ections such as angioneurotic edema, se reactions such as angioneurotic edema, ser-rum suckness and anaphylaxis have been re-ported, some of these in patients known to be sensitive to penicillin. If an allergic reac-tion should occur, the drug should be dis-continued and the usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment.

Skin and Mucous membranes-Skin rashes, urticaria and vaginitis and rare instances

dricaria and vaginus and rare instances of exfoliative and vesiculobullous dermatitis have been reported.

Liver -Although no direct relationship of Lincorn (lincomycin hydrochloride monohydrate) to liver dysfunction has been established, jaundice and abnormal liver function tests (particularly elevations of serum trans-aminase) have been observed in a few in-

stances, Cardiovascular — Instances of hypotension following parenteral administration have been reported, particularly after too rapid intravenous administration, Rare instances of cardiopolimonary arrest have been reported after too rapid intravenous administration, (See "Dosage and Administration").

Local Reactions — Patients have demonstrated excellent local tolerance to intra-muscularly administered Lincocin (Lacomyem hydrochloride monohydrate). Reports following injection have been infre-

Intravenous administration of Lincocin in 250 to 500 ml, 6.) percent glucose in dis-filled water or normal saine produced no-local irrutation or pulconis. Dosage and Administration:

Ocal—Adults: Mild to moderately severe in-lections—500 mg, 3 times per day (500 mg, approximately every 8 hours). Severe infec--500 mg, or more 4 times per emg, or more approximately every (500 mg, or more approximately every 6 hours). Children over 1 month of age: hours). Children over 1 month of ages Mild to moderately severe infections—30 ng./kg./day (15 ng./lb./day) divided into 3 or 4 equal doses. Severe infections—60 ng./kg./day (30 ng./kg./day) divided into 3 or 4 equal doses.

NOTE: For optimal absorption it is reconmended that nothing be given by mooth except water for a period of one to two 'our, before and after oral administration

Intermuscular-Adults: Mild to moderately severe infections—600 mg. (2 cc.) intra-muscularly every 24 hours. Severe infections —600 mg. (2 cc.) intramuscularly every 12 hours or more often.

Children over I month of age: Mild to moderately severe infections—one intramuscular injection of 10 mg/kg. (5 mg/lo.) every 24 hours. Severe infections—one intramuscuhar injection of 10 mg./kg. (5 mg./lb.) every 12 hours or more often.

Intravenous-Adults: 600 mg. (2 cc.) intravenously every 8 to 12 hours. For intra-venous administration, Lincocin should be added to 250 ec, or more of 5 percent glu-cose in water or normal saline and given as an infusion. When doses of 4 grams or more an infusion. When doses of 4 grains of more are given, Lincocion (lincomycin hydrochloride monohydrate) should be diluted in 500 ec. of fluid and administered at a rate not to exceed 100 ec. per hour. Children over 1 month of age: 10 to 20 mg./kg./day (5 to 10 mg./lb./day) divided into 2 or 3 doses and seem of the property of the conditions of the condition of and given as an infusion at 8 to 12 hour intervals. The method of administration is the same as noted above for adults.

NOTE: For more serious infections, doses may have to be increased, in threatening situations, doses of as much trans daily have been given parenterally to

adults.
With \(\beta\)-hemolytic streptococcal infections, treatment should continue for at least 10 days to diminish the likelihood of subsequent rheumatic fever or glomerulonephritis.

Patients with diminished renal function; When Lincoch therapy is required in individuals with severe impairment of renal function, an appropriate dose is 25 to 30% of that recommended for patients with normally functioning kidneys.

How Supplied: Lincocin is available as:

Capsules 250 mg. Pediatric Capsules, each capsule contains linconycin hydrochloride monohydrate equivalent to linconycin base 250 parties of 24 and 100. 550 mg, each capsule contains lineony-cin hydrochloride monohydrate equivalent to lineomycin base 500 mg.—supplied in bottles of 24 and 100.

Sterile Solution, each ce, contains lincomy-Sterile Solution, each cc. contains hiscomycin hydrochloride monohydrate equivalent to lincomycin base 300 mg.; also lienzyl Alcohol, 9 mg.—supplied in single dose 2 cc. syringe, 2 cc. vials, and 10 cc. vials. Syrup, each 5 cc. (teaspoonful) contains lincomycin hydrochloride monohydrate equivalent to lincomycin base 250 mg.—swedded to 60 cc. and ent buttles. supplied in 60 cc. and pint bottles.

Animal Pharmacology: In vivo experimental Animal Pharmacology: In vivo experimental animal studies demonstrated Lines his effectiveness in protecting animals infected with Streptococcus viridans, B-hemolytic Streptococcus, Micrococcus aureus, Diplococcus pneumoniae and Leptospira pomona. It was ineffective in Klebsiella, Pasteurella, Pseudomonas, Salmonella and Shigella infections, Clinical Studies: Experience with 345 obstetrical patients receiving this drug revealed no ill effects related to pregnarcy. LINCOCINO

(Lincomycin Hydrochloride, U.S.P.) Capsules, 500 mg. 100's

Military Stock # FSN 6505-912-2404 VA Stock # FSN 6505-912-2404A. Storile Solution, 300 mg./ml., 10 ml.: Military Stock # FSN 6505-926-4768 VA Stock # FSN 6505-943-4374A.

Description: Lincomycin Hydrochloride is the monohydratea salt of lincomycin, a substance produced by the growth of a member of the lincolnensis group of Streptomyces Lincolnensis (Fam. Streptomycetaceae). It is a white, or practically white, crystalline powder. It is odorless or has a faint odor. Its solutions are acid and are dextrorotary. Lincomycin Hydrochloride is freely soluble in water; soluble in dimethylformamide and very soluble in acetone.

Actions: Microbiology-Lincocin has been shown to be effective against most of the common gram-positive pathogens. Depending or the sensitivity of the organism and concentration of the antibiotic, it may be either bactericidal or bacteriostatic. Cross resistance has not been demonstrated with penicillin, chloramphenicol, ampicillin, cephalosporins or the tetracyclines. Despite chemical differences, lincomycin exhibits antibacterial activity similar to but not identical with the macrolide antibiotics (e.g. crythroi yein). Some cross resistance (with crythron yein) including a phenomenon known as dissociated cross resistance or macrolide effect has been re-ported. Microorganisms have not developed resistance to Lincocin rapidly when tested by in vitro or in vivo methods. Staphylococci develop resistance to Lincocin in a slow, stepwise manner based on in vitro, serial subculture experiments. This pattern of resistance development is unlike that shown for strepto-

Studies indicate that I inc cin a mycin hydrochloride menohydral, do. share an-

tigenicity with penicillin compounds.
Biological Studios In vitro studios indicate
that the spectrum of activity includes Micrococcus (Staphylococcus) aureus, Staphylococcus albus, Bhemolytic Streptococcus, Streptococcus viridans, Diplococcus pneumoniae,
Clostridium tetani, Clostridium perfringens,
Corynebacterium diphtheriae and Corynebacterium acnes.

NOTE: The drug is not active against most strains of Streptococcus faecalis, nor against Neisseria gonorrhoeae, Hemophilus influenzae, or other gram-negative organisms or veasts.

Human Pharmacology—Lincocin is absorbed rapidly after a 500 mg. oral dose, reaching peak levels in 2 to 4 hours. Levels are maintained above the MIC (minimum inhibitory concentration) for most gram-positive organisms for 6 to 8 hours. Urinary recovery of drug in a 24-hour period ranges from 1.0 to 31 percent (mean: 4.0) after a single oral dose of 500 mg. Tissue level studies indicate that bile is in important route of exerction. Significant levels have been demonstrated in the majority of body tissues. Although the drug is not present in significant amounts in the spinal fluid of normal volunteers, it has been demonstrated in the spinal fluid of one patient with pneumococcal meningitis.

Intramuscular administration of a single dose of 600 mg, produces a peak serum level at 30 minutes with detectable levels persisting for 24 hours. Urinary excretion after this dose ranges from 1.8 to 24.8 percent (mean: 17.3). The intravenous infusion over a 2-hour interact of 600 mg, of Lincocir (lincomycin hydrochloride monohydrate) in 500 ml, of 5 percent glucose in distilled water yields therapeutic levels for 14 hours. Urinary exerction ranges from 4.9 to 30.3 percent (mean: 13.8).

The biological half-life, after oral, intramuscular or intravenous administration is 5.4 +1.0 hours.

Indications: Lincocin is indicated in infections due to susceptible strains of streptococci, pneumococci and star-hylococci. As with all antibiotics, in vitro susceptibility studies should be performed.

Lincocin has been demor a alted to 1's effective in the treatment of staphylococal fections resistant to other antibiotics and apprible to lincomycin. St. Lylococal strons resistant to Lincocin have been recovered; culture and susceptibility studies should be done in conjunction with Lincocin ther. by. In the case of macrolides, partial bu complete cross resistance may occur (see Microbiology'). The drug may be administered concomitantly with other antimicrobial agents when indicated.

Contraindications: This drug is contraine, cated in patients previously found to be hypersensitive to lincomycin or clindamycin. It is not indicated in the treatment of minor bacterial infections or viral infections.

WARNINGS: CASES OF SEVERE AND PER-SISTENT DIARRHEA HAVE BEEN REPORTED AND HAVE AT TIMES NECESSITATED DIS-CONTINUANCE OF THE DRUG. THIS DIAR-RHEA HAS BEEN DCCASIONALLY ASSOCI-ATED WITH BLOOD AND MUCUS IN THE STOOLS AND HAS AT TIMES RESULTED IN AN ACUTE COLITIS. THIS SIDE EFFECT USU-

Continued on next page

Information on those Upjohn products is based on labelling in effect on July 1, 1971. Further information on desage and administration, side effects, precautions and contraindications for these and other Upjohn products may be obtained from either the package brochure or Medical Services, The Upjohn Company, Kalamazoo, Michigan.

Product Information

Always consult Supplement

Upjohn-Cont.

ALLY HAS BEEN ASSOCIATED WITH THE ORAL DOSAGE FORM BUT OCCASIONALLY HAS BEEN REPORTED FOLLOWING PAREN-TERAL THERAPY.

A careful inquiry should be made concerning previous sensitivities to drugs and other al-

Usage in Prognancy-Safety for use in preg-

nancy has not been established. Usago in Nawborn—Until further clinical experience is obtained, Lincocin is not indicated in the newborn.

Precautions: Lincocin (lincomycin hydrochloride monohydrate), like any drug, should be used with caution in patients with a history of asthma or significant allergies

The use of antibiotics occasionally results in overgrowth of nonsusceptible organismsparticularly yeasts. Should sup rinfections occur, appropriate measures should be taken. When patients with pre-existing monilial infections require Lincocin therapy, concomitant antimonilial treatment should be given. During prolonged Lincocin therapy, periodic liver function studies and blood counts should be performed.

Since adequate data are not yet available in patients with pre-existing liver disease, its use in such patients is not recommended at this time unless special clinical circumstances

Adverse Reactions:

Gastrointestinal-Glossitis, stomatitis, nausea, vomiting Persistent diarrhea, enterocolitis and pruritus ani. (See "Warnings"). Homopoiotic-- Neutropenia, leukopenia, agranulocytosis and thrombocytopenic purpura have been reported

Hypersonsitivity Reactions-Hypersensitivity actions such as angioneurotic edema, serum sickness and anaphylaxis have been reported, some of these in patients known to be nsitive to penicillin. If an allergic reaction should occur, the drug should be discontinued and the usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment.

Skin and Mucous Membranes-Skin rashes, urticaria and vaginitis and rare instances of exfoliative and vesiculobullous dermatitis have been reported.

Liver-Although no direct relationship of Liv cocin (lincomycin hydrochloride monohy-drate) to liver dysfunction has been established, jaundice and abnormal liver function tests (particularly elevations of serum transaminase) have been observed in a few in-

Cardiovascular-Instances of hypotension following parenteral administration have been reported, particularly after too rapid intravenous administration. Rare instances of cardiopulmonary arrest have been reported after too rapid intravenous administration. (See "Dosage and Administration").

Special Senses-Tinnitus and vertigo have been reported occasionally.

Local Reactions-Patients have demonstrated excellent local tolerance to intramuscularly administered Lincocin (lincomycin hydrochloride monohydrate). Reports of pain following injection have been infrequent.

Intravenous administration of Lincocin in 250 to 500 ml. of 5 percent glucose in distilled water or normal saline produced no local irritation or phlebitis.

Dosage and Administration:

Oral-Adults: Mild to moderately se or infecons-500 mg. 3 times per day (50t ps ; approximately every 8 hours). Severe infections-500 mg. or more 4 times per day (500 mg. or more approximately every 6 hours). Children over 1 month of age: Mild to moder-

ately severe infections-30 mg./kg./day (15 mg./lb./day) divided into 3 or 4 equal doses Severe infections--00 mg./kg./day (30 mg./ lb./day) divided into 3 or 4 equal doses.

NOTE: For optimal absorption it is recommended that nothing be given by mouth except water for a period of one to two hours before and after oral administration of Lincocin.

Is tramuscular-Adults: Mild to moderately sehere infections-600 mg. (2 ml.) intramuscularly every 24 hours. Severe infections-600 mg. (2 ml.) intramuscularly every 12 hours or more often. Children over 1 month of age: Mild to moderately severe infections-one intramuscular injection of 10 mg./kg. (5 mg./ (b.) every 24 hours. Severe infections-one intramuscular injection of 10 mg./kg. (5 mg./ lb.) every 12 hours or more often.

Intravenous—Adults: 600 mg. (2 ml.) intravenously every 8 to 12 hours. For intravenous administration, Lincocin should be added to 250 cc. or more of 5 percent glucose in water or normal saline and given as an infusion. When doses of 4 grams or more are given, Lincocin (lincomycin hydrochloride monohydrate) should be diluted in 500 mi. of fluid and administered at a rate not to exceed 100 ml. per hour. Children over 1 month of age: 10 to 20 mg./kg./day (5 to 10 mg./lb./day) divided into 2 or 3 doses and given as an infusion at 8 to 12 hour intervals. The method of administration is the same as noted above for adults

NOTE: For more serious infections, these doses may have to be increased. In life-threat-ening situations, doses of as much as 8 grams daily have been given parenterally to adults. With β-hemolytic streptococcal infections, treatment should continue for at least 10 days to diminish the likelihood of subsequent rheumatic fever or glomerulonephritis

Patients with diminished renal function: When Lincocin therapy is required in individuals with severe impairment of renal function, an appropriate dose is 25 to 30% of that recommended for patients with normally functioning kidneys

How Supplied: Lincocin is available as:

Capsulos

250 mg. Pediatric Capsules, each capsule contains lincomycin hydrochloride monohydrate equivalent to lincomycin base 250 mg.-supplied in bottles of 24 and 100.

24's NDC 9-336-1 100's NDC 9-336-2

500 mg., each capsule contains lincomycin hydrochloride monohydrate equivalent to lincomycin base 500 mg.—available in bottles of 24 and 100. Also Unit-Dose Package Foil Strip of 100 capsules

24's NDC 9-500-1 100's NDC 9-500-2 Foil Strip NDC 9-500-3

Storile Solution, each ml. contains lincomycin hydrochloride monohydrate equivalent to lincomycin base 300 mg.; also benzyl alcohol, 9 mg., water for injection, q.s .- available in disposable 2 ml. syringes, and in 2 ml. and 10 ml. vials. Also available in 3.34 ml. and 6.67 ml. vials containing lincomycin hydrochloride monohydrate equivalent to 1 and 2 gms. respectively of lincomycin base. The latter vials are filled below capacity to facilitate transfer of the contents by means of the included transfer needle into an infusion bottle.

2 ml. Syringe NDC 9-600-1 2 ml. Vial NDC 9-555-1 10 ml. Vial NDC 9-555-2 3.34 mt. Vial NDC 9-555-3 6.67 ml. Vial NDC 9-555-4

Syrup, each 5 ml. (teaspoonful) contains lincomycin hydrochloride monohydrate equivalent to lincomycin base 250 mg.-available in 60 ml, and pint bottles.

60 ml. NDC 9-444-1 Pint NDC 9-444-2 [Shown in Product Identification Section]

Animal Pharmacology: In vivo experimental animal studies demonstrated Lincocin's effectiveness in protecting animals infected with Streptococcus viridans, B-hemolytic Streptococcus, Micrococcus aureus, Diplococcus pneumoniae and Leptospira pomona. It ineffective in Klebsiella, Pasteurella, Pseudomonas, Salmonella and Shigella infec-

Clinical Studies: Experience with 345 obstetrical patients receiving this drug revealed no ill effects related to pregnancy.

of the lincolnensis group of Streptomyces lincolnensis (Fam. Streptomycetaceae). It is a white, or practically white, crystalline powder and is odorless or has a faint odor. Its solutions are acid and are dextrorotatory. Lincomycin Hydrochloride is freely soluble in water; soluble in dimethylformamide and very slightly soluble in acetone.

Actions: Microbiology-Lincocin has been shown to be effective against most of the common gram-positive pathogens. Depending on the sensitivity of the organism and concentration of the antibiotic, it may be either bactericidal or bacterios tic. Cross resistance has not been demonstrated with penicillin, chloramphenicol, ampiciilin, cephalosporins or the tetracyclines. Despite chemical differences, lincomycin exhibits antibacterial activity similar but not identical to the macrolide antibiotics (e.g. erythromycin). Some cross resistance (with erythromycin) including a phenomenon known as dissociated cross resistance or macrolide effect has been reported. Microorganisms have not developed ance to Lincocin rapidly when tested by in vitro or in vivo methods. Staphylococci develop resistance to Lincocin in a slow, step-wise manner based on in vitro, serial subculture experiments. This pattern of resistance development is unlike that shown for streptomy-

Studies indicate that Lincocin (lincomycin hydrochloride) does not share antigenicity with ponicillin compounds.

Biological Studios—In vitro studies indicate that the spectrum of activity includes Micrococcus (Staphylococcus) aurcus, Staphylococcus albus, B-hemolytic Streptococcus, Streptococcus viridans, Diplococcus pneumoniae, Clostridium tetani, Clostridium perfringers, Corynebacterium diphtheriae and Corynebacterium acnes.

NOTE: The drug is not active against most strains of Streptococcus faccalis, nor against Neisseria gonorrhocae, Neisseria meningitidis, Hemophilus influenzae, or other gramnegative organisms or yousts.

Human Pharmacology—Lincocin is absorbed rapidly after a 500 mg oral dose, reaching peak levels in 2 to 4 hours. Levels are maintained above the MIC (minimum inhibitory concentration) for most gram-positive organisms for 6 to 8 hours. Urinary recovery of drug in a 24-hour period ranges from 1.0 to 34 percent (mean: 4.0) after a single oral dose of 500 mg. Tissue level studies indicate that bile is an important route of excretion. Significant levels have been demonstrated in the majority of body tissues. Although the drug is not present in significant amounts in the spinal fluid of normal volunteers, it has been demonstrated in the spinal fluid of one patient with pneumococcal meningitis.

Intramuscular administration of a single dose of 600 mg produces a peak serum level at 30 minutes with detectable levels persisting for 24 hours. Urinary excretion after this dose ranges from 1.8 to 24.8 percent (mean: 17.3). The intravenous infusion over a 2-nour interval of 600 mg of Lincocin (linconycin hydrocroide) in 500 ml of 5 percent glucose in distilled water yields therapeutic levels for 14 hours. Urinary excretion ranges from 4.9 to 30.3 percent (mean: 13.8).

The biological half-life, after oral, intramuscular or intravenous administration is 5.4 +1.0 hours.

Hemodialysis and peritoneal dialysis do not effectively remove lincomycin from the blood.

Indications: Lincocin is indicated in infections due to susceptible strains of streptococci, pneumococci and staphylococci. As with all antibiotics, in vitro susceptibility studies should be performed.

Lincocin has been demonstrated to be effec-

tive in the treatment of staphylococcal infections resistant to other antibiotics and susceptible to lineomycin. Staphylococcal strains resistant to Lincocin have been recovered; culture and susceptibility studies should be done in conjunction with Lincocin therapy. In the case of macrolides, partial but not complete cross resistance may occur (see Microbiology). The drug may be administered concomitantly with other antimicrobial agents when indicated.

Contraindications: This drug is contraindicated in patients previously found to be hypersensitive to lincomycin or clindamycin. It is not indicated in the treatment of minor bacterial infections or viral infections.

WARNINGS: CASES OF SEVERE AND PER-SISTENT DIARRHEA HAVE BEEN REPORTED AND HAVE AT TIMES NECESSITATED DIS-CONTINUANCE OF THE DRUG. THIS DIAR-RHEA HAS BEEN OCCASIONALLY ASSOCI-ATED WITH BLOOD AND MUCUS IN THE STOOLS AND HAS AT TIMES RESULTED IN AN ACUTE COLITIS. THIS SIDE EFFECT USU-ALLY HAS BEEN ASSOCIATED WITH THE ORAL DOSAGE FORM BUT OCCASIONALLY HAS BEEN REPORTED FOLLOWING PAREN-TERAL THERAPY.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens.

Usago in Prognancy-Safety for use in pregnancy has not been established.

Usage in Nowborn—Until further clinical experience is obtained, Lincocin is not indicated in the newborn.

Precautions: Lincocin (lincomycin hydrochloride), like any drug, should be used with caution in patients with a history of asthma or significant allergies.

The use of antibiotics occasionally results in overgrowth of nonsusceptible organisms—particularly yeasts. Should superinfections occur, appropriate measures should be taken. When patients with pre-existing monilial infections require Lincocir, therapy, concomitant antimonilial treatment should be given. During prolonged Lincocin therapy, periodic liver function studies and blood counts should be performed.

Since adequate data are not yet available in patients with pre-existing liver disease, its use in such patients is not recommended at this time unless special clinical circumstances so indicate.

In experimental animals, high doses of lincomycin have been shown to have neuromuscular blocking properties which are not reversed by neostigmine. Other animal studies have shown that there can be an additive effect or potentiation when lincomycin is given concurrently with d-tubocurarine.

Adverse Reactions:

Gastrointostinal—Glossitis, stomatitis, nausea, vomiting. Persistent diarrhea, enterocolitis and pruritus ani. (See "WARNINGS"). Homatopoiotic: Neutropenia, ieukopenia,

Homatopoiotic: Neutropenia, ieukopenia, agranulocytosis and thrombocytopenic purpura have been reported. There have been rare reports of aplastic anemia and pancytopenia in which Lincocin could not be ruled out as the causative agent.

Hyporsonsitivity Reactions—Hypersensitivity reactions such as angioneurotic edema, serum sickness and anaphylaxis have been reported, some of these in patients known to be sensitive to penicillin. If an allergic reaction should occur, the drug should be discontinued and the usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment.

Skin and Mucous Membranes—Skin rashes, urticaria and vaginitis and rare instances of exfoliative and vesiculobullous dermatitis have been reported.

LINCOCIN⁴⁰
(Lincomycin Hydrochlorido, U.S.P.)
CAPSULES, STERILE SOLUTION, SYRUP
500 mg C-psulos (100's):
Military Stock # FSN 6505-912-2404
VA Stock # FSN 6505-912-2404A

VA Stock # FSN 6505-912-2404A Storile Solution, 300 mg/ml (10 ml): Military Stock # FSN 6505-926-4768 VA Stock # FSN 6505-943-4374A

Description: Lincomycin Hydrochloride is the monohydrated salt of lincomycin, a substance produced by the growth of a member Livor—Although no direct relationship of Lincocin (lincomycin hydrochloride) to liver dysfunction has been established, jaundice and abnormal liver function tests (particularly elevations of serum transaminase) have been observed in a few instances.

Cardiovascular—Instances of hypotension following parenteral administration have been reported, particularly after too rapid intraverous administration. Rare instances of cardiopulmonary arrest have been reported after too rapid intravenous administration. (See Dosago and Administration).

Special Sonsos—Tinnitus and vertigo have been reported occasionally.

Local Reactions—Patients have demonstrated excellent local tolerance to intramuscularly administered Lincocin (lincomycin hydrochloride). Reports of pain following in-

jection have been infrequent. Intraveneus administration of Lincocin in 250 to 500 mi of 5 percent glucose in distilled water or normal saline produced no local irritation or phlebitis.

Dosage and Administration:

Otal—Adults: Mild to moderately severe infections—500 mg 3 times per day (500 mg approximately every 8 hours). Severe infections—500 mg or more 4 times per day (500 mg or more approximately every 6 hours). Children over 1 month of age: Mild to moderately severe infections—30 mg/kg/day (1: mg/ib/day) divided into 3 or 4 equal doses. Severe infections—60 mg/kg/day (30 mg/ib/day) divided into 3 or 4 equal doses.

With β-hemolytic streptococcal infections, treatment should continue for at least 10 days to diminish the likelihood of subsequent rhemmatic fever or giomerulonephritis.

NOTE: For optimal absorption it is recommended that nothing be given by mouth except water for a period of one to two hours before and after oral administration of Lincotin.

Intramuscular—Adults: Mild to moderately severe infections—600 mg (2 ml) intramuscularly every 24 hours. Severe infections—600 mg (2 ml) intramuscularly every 12 hours or more often. Chikiron over 1 month of ago:
Mild to moderately severe infections—one intramuscular injection of 10 mg/kg (5 mg/lb) every 24 hours. Severe infections—one intramuscular injection of 10 mg/kg (5 mg/lb) every 12 hours or more often.

Intravenous—Adults: The intravenous dose will be determined by the severity of the infection. For moderately severe infections doses of 600 mg (2 ml) to 1 gm are given every 8-12 hours. For more serious infections these doses may have to be increased. In lifethreatening situations daily intravenous doses of as much as 8 grams have/see given. Intravenous doses are given on the basis of 1 gm of Lincocin diluted in not loss than 100 ml of appropriate solution and infused over a period of not less than one hour.

Doso	Vol. Diluont	Time
600 mg	100 ml	1 hr
1 gm	100 ml	1 hr
2 gm	200 ml	2 hr
3 jan	300 ml	3 hr
4 gm	400 ml	4 hr

These doses may be repeated as often as required to the limit of the maximum recommended daily dose of 8 gm.

Children over 1 month of age: 10-20 mg/kg/ day (5-10 mg/lb/day) depending on the severity of the infection may be infused in divided doses as described above for adults.

NOTE: Severe cardiopulmonary reactions have occurred when this drug has been given at greater than the recommended concentration and rate.

Subconjunctival Injection—0.25 ml (75 mg) injected subconjunctivally will result in ocular

Physical Compatibilities:

Physically Compatible With:

Physically compatible for 24 hours at room temperature unless otherwise indiced Infusion Solutions

Antibiotics in Infusion Solutions

Infusion Solutions
Dextrose in Water, 5% and 10%
Dextrose in Saline, 5% and 10%
Ringer's Solution
Sodium Lactate 1/6 Molar
Travert 10%—Electrolyte No. 1
Dextran in Saline 6% w/y

Travert 10%—Electrolyte No. 1
Dextran in Saline 6% w/v
Vitamins in Infusion Solutions
B-Complex
B-Complex with Ascorbic Acid

Colistimethate (Satisfactory for 4 hours) Ampleillin Methicillin Chloramphenicol Polymyxin B Sulfate

Cephalothin Tetracycline HCl

Penicillin G Sodium (Satisfactory

Physically Incompatible With: Novobiocin Kanamycin

T SHOULD BE EMPHASIZED THAT THE COMPATIBLE AND INCOMPATIBLE DETERMINATIONS ARE PHYSICAL OBSERVATIONS ONLY, NOT CHEMICAL DETERMINATIONS, ADEQUATE CLINICAL EVALUATION OF THE SAFETY AND EFFICACY OF THESE COMBINATIONS HAS NOT BEEN PERFORMED.

fluid levels of antibiotic (lasting for at least 5 hours) with MiC's sufficient for most susceptible pathogens.

Pations with diminished ronal function: When Lincocin therapy is required in individuals with severe impairment of renal function, an appriate dose is 25 to 30% of that recommended for patients with normally functional hidness.

ctow Supplied: Lincorin is available as: 250 mg Podiatric Capsulos: Each capsule contains lincomycin hydrochloride monohydrate equivalent to lincomycin base 250 mg.

equivalent to lincomycin base 250 mg.

Bottles of 24 NDC 9-336-1

Bottles of 100 NDC 9-336-2

500 mg Capsules: Each capsule contains lin-

comycin hydrochloride monohydrate equivalent to lincomycin base 500 mg.

Bottles of 24 NDC 9-500-1

Bottles of 100 NDC 9-500-2

Foil Strip (100) NDC 9-500-3
Storilo Solution: Each ml contains lincomycin hydrochloride monohydrate equivalent to lincomycin base 300 mg, also Benzyl Alcohol, 9 mg, Water for injection, es—available in single dose 2 ml syringes, in 2 ml and 10 ml vials. Also available in 3.34 ml and 6.67 ml vials containing lincomycin hydrochloride monohydrate equivalent to 1 and 2 grams respectively, of lincomycin base. The latter vials are filled below capacity to facilitate transfer of the contents, by means of the included trans-

fer needle, into an infusion bottle.

2 ml U-Ject NDC 9-600-1
(Disposable Syringe)
2 ml vial NDC 9-555-1
10 ml vial NDC 9-555-2
3.34 ml vial NDC 9-555-3

(1 Gm hospital package) 6.67 ml vial NDC 9-555-4

(2 Gm hospital package)
For information on suggested administration
techniques, see package insert.

Syrup: Each 5 ml (teaspoonful) contains lincomycin hydrochloride monohydrate equivalent to lincomycin base 250 mg.

60 ml bottles NDC 9-444-1 Pint bottles NDC 9-444-2

Animal Pharmacology: In vivo experimental animal studies demonstrated the effectiveness of Lincocia in protecting animals infected with Streptococcus viridans, B-hemolytic Streptococcus, Micrococcus aureus, Diplococcus pneumoniae and Leptospira pomona. It was ineffective in Klebsiella, Pasteurella, Pseudomonas, Salmonella and Shigella infec-

Clinical Studies: Experience with 345 obstetrical patients receiving this drug revealed no ill effects related to prognancy.

See table above.]

[Capsules Shown in Product Identification Section]

Upjohn Company, The KALAMAZOO, MICH. 49001

LINCOCIA(I)
(Lincomycin Hydrochloride, U.S.P.)
CAPSULES, STERILE SOLUTION, SYRUP

Prescribing information for this product, which appears on pages 1498-1499 of the 1974 PDR, has been revised as outlined below. Write "See Supplement B" alongside product heading. Wavering: Lamedi dely preceding Pescription and following the product title, a boxed WARN-ING statement has been inserted. This replaces the previous paragraph in the Waverings section relative to diarchea and colitis. The new statement reads as follows:

WARNING

Severe and persistent diarrhea, which may be accompanial by blood and mucus, and which may be associated with changes in large bowel mucosa diagnosed as "pseu-domembranous colitis", has been reported in association with the administration of

Lincocin (lincomycin hydrochloride). When significant diarrhea occurs (usually more than 5 bowel movements daily), the drug should be discontinued or, if necessary, continued only with close observa-tion of the patient (large bowel endoscopy has been recommended). Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte and protein supplementation as indicated. Antiperistaltic agents—opiates, meperi-dine, and diphenoxylate with atropine may prolong and/or worsen the condition. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered. Note: Diarrhea has been observed to begin up to several weeks following cessation of therapy with Lincocin. The physician must be alert to this possibility.

Previous The last paragraph of the Pre-cautions statement has been amended to read: Lincomycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuronuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents. Donage and Administration: The following paragraph has been added at the beginning of this section:

If significant diarrhea occurs during therapy, this antibiotic should be discontinued. (See VARNING box).

SUMMARY OF EXHIBITS 16 - 65

EXHIBIT	DATE	NO. OF CASES	DIAGNOSIS	UPJOHN REPORT TO FDA
16	4/66	1	Fulminating ulcerative colitis	Colitis
17		2	Acute fulmin- ating ulcer- ative colitis	Colitis
18	3/65	1	Colitis of 5 months dura- tion	'Protracted diarrhea''
19	5/66	1	Picture simu- lating mild acute ulcer- ative colitis	Colitis
19	5/66	1	Bowel typical of acute co- litis with erythema, mucus and blood	Colitis
20	2/65	1	Non-specific colitis	Diarrhea
20	5/65	1	Ulcerative colitis	Diarrhea
20	6/65	1	Acute ulcer- ative colitis with edema of the mucus; friability; ulcerations, purulent dis- charge and bleeding	Diarrhea
21	2/65	1	Acute ulcera- tive colitis; subsequently developed toxic mega- colon, then	Colitis

EXHIBIT	DATE	NO. OF CASES	DIAGNOSIS	UPJOHN REPORT TO FDA
			hemorrhaged and had sub- total colec- tomy and ileostomy	
21	1/66	1	Typical ulcerative colitis; hemorrhage and toxic colon	Colitis
22	11/66	1	Non-specific ulcerating colitis; colon resection	Non-specific ulcerating colitis
23	12/65	1	Ulcerative colitis	Colitis
24	3/68	2	Acute abdomen; colon of beefy, red, granular consistercy	'Diarrhea''
25	6/66	1	Bloody stools; colitis-like reaction	Severe diarrhea with a colitis- like reaction
26	2/66	1	enterocolitis; acute febrile episode with probable ulceration of bowel; possibility of early ulcerative colitis despite negative sigmoidoscopic and barium enema study	Diarrhea and enterocolitis; Doctor stated possibility of early ulcerative colitis despite negative sigmoidoscopic and barium study

			DT.1000000	UPJOHN
EXHIBIT	DATE	NO. OF CASES	DIAGNOSIS	REPORT TO TOA
27	10/66	1	Granular bowel mucosa; numer- ous ulcers in cecum	"Intractable diarrhea" and abdominal mass
28	4/66	1	Colitis	Diarrhea
29		1	Acute colitis and proctitis	Colitis
29		1	Sub-acute colitis	Colitis
29		1	Appearance of chronic ulcerative colitis	Colitis
30	8/69	1	Ulcerative colitis	Colitis
31	6/65	1	Ulcerative proctitis	Diarrhea
32	3/65	1	Proct colitis; mild ulcera- tion of rectal mucosa	Diarrhea
32	2/65	1	Proctitis	Diarrhea
32	5/65	. 1	Ulceration of rectal mucosa similar to that seen in chronic ulcer- ative colitis	Diarrhea
33	6/66	1	Colitis	Colitis
34	12/66	1	Ulcerative colitis	Diarrhea and colitis

EXHIBIT	DATE	NO. OF CASES	DIAGNOSIS	UPJOHN REPORT TO FDA
35	6/68	1	Non-specific ulcerative colitis	Diarrhea and colitis
36	4/67	1	Ulcerative colitis with bleeding	Colitis
37	8/68	1	Severe diar- rhea; streaks of blood; changes of ulcerative colitis	Colitis
38	1/66	1	Edema of rectum and lower sigmoid with mucosa almost completely covered with small pustular ulcerations	Diarrhea
39	2/68	1	Ulcerative colitis	Diarrhea
40	6/66	2	Non-specific ulcerative colitis	Colitis
41	1/68	1	Ulcerated lesions of the bowel with punctate hemorrhage	Colitis
42	12/67	1	Ulcerative and inflamed polypoid mucosa; ulcer- ative colitis	Proctitis

EXHIBIT	DATE	NO. OF CASES	DIAGNOSIS	UPJOHN REPORT TO FDA
43	8/68	1	Non-specific colitis	Diarrhea with colitis
44	1/66	1	Gross proctitis	Diarrhea
44	8/66	1	Gross proctitis	Diarrhea
44	12/65	1	Severe proctitis; pus filled ulcers	Diarrhea

All three cases in Exhibit 44 had ulcerations of

the bowel

1 45 Ulcerative(?) Diarrhea in 50% of patients colitis; over 50 patients (50%) have had some form of diarrhea varying from 3-4 days of loose stools to almost prostration from intractable diarrhea 46 1/66 1 Spastic Diarrhea colitis; swollen rectal and sigmoid

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1

47

48

10/66

11/66

mucosa with much blood and mucus present and some denuded areas

Severe colitis

Hemorrhagic

colitis

Diarrhea

Diarrhea

EXHIBIT	DATE	NO. OF CASES	DIAGNOSIS	UPJOHN REPORT TO FDA
49	12/65	1	Colitis	Protracted Diarrhea
50	4/65	1	Acute colitis	Persistent Diarrhea
51	6/65	1	Proctitis and colitis, acute without ulceration	Severe Diarrhea
51	6/65	1	Acute colitis with exudate but no ulcers	Severe Diarrhea
52	10/68	1	Bloody diarrhea and colitis	Bloody Diarrhea
53	1/69	1	Colitis-like condition	Colitis
54	2/66	1	Mucus colitis; diarrhea for 15 mos.	Diarrhea
54	3/66	1	Mucus colitis; diarrhea for 1 yr.	Diarrhea
55	11/67	1	Mucus colitis	Diarrhea and colitis
56	9/68	1	Presistent mucus colitis	Gastroenteritis
57		3	Colitis	Colitis
58	4/66	1	Bloody diarrhea	Diarrhea
59	1969	1	Colitis	Colitis
60	4/69	1	Colitis	Colitis-type reaction

EXHIBIT	DATE	NO. OF CASES	DIAGNOSIS	UPJOHN REPORT TO FDA
61	9/66	1	Colitis	Diarrhea
62	1966	1	Colitis (reported by patient)	No report furnished
63	8/69	1	Ulcerative colitis; 6 lb. weight loss	Diarrhea with colitis
64	3/65	1	Colitis	Diarrhea
65	6/65	1	Colitis	Severe diarrhea

Drummond Medical Group

1111 NORTH CHINA LAKE BOULEVALD-RIDGECREST, CALIFORNIA

TELEPHONE FR 5-4421

April 7, 1966

Medical Services
The Upjohn Company
Kalamazoo, Michigan

Dear Dr. Angell:

Thank you for your letter of March 29, 1966, in reference to an instance of diarrhea associated with the use of Lincocin. At the outset, I would like to correct the report you apparently received from your representative in Los Angeles. The case in question was not one of uncomplicated diarrhea, but rather a case of fulminating ulcerative colitis.

This is a 46 year old nurses aide who was exposed to a case of meningococcic meningitis for which she was given a course of Lincocin, since she was allergic to Penicillin. The patient developed diarrhea after four capsules of Lincocin which was rather mild at the onset. In spite of this, she continued the drug until a total of 18 capsules were used which intensified the diarrhea and also caused abdominal cramping and tenesmus. The diarrhea did not abate and became gradually worse. The patient was admitted to the hospital three weeks after having been given the bincocin. Her signs and symptoms were consistent with a severe case of ulcerative colitis affecting the entire colon but sparing the rectum. Sigmoidoscopy only showed hyperemia without ulcers. The patient responded well to instituted treatment and has been diagranged from the hospital. She is still followed on the outside and maintained on corticosteroids and Azulfidine.

Her past history reveals that she has been in good health except for hay fever for which she is being desensitized. She has no history of having had any intestinal disease or condition. She has been quite nervous and under some domestic stress for the past six months.

The administration of Lincocin might be entirely a coincidental factor. On the other hand, the timing is quite suggestive that Lincocin must have had some triggering effect; maybe in the sense of another immune mechanism. This patient should have stopped the drug after developing diarrhea initially. I feel that this case warrants your attention. I wonder if there have been any other cases of alcerative colitis in connection with the administration of this drug. I remain

Sincerely yours,

Kurt A. de Crinis, M.D. Dept. of Internal Medicine PLAINTIFF EXHIBIT

THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

April 14, 1966

Raymond E. Berzilai, M.D. Division of New Drugs Antibiotic Drug Branch Pureau of Medicine Food and Drug Administration Washington, D. C. 20204

Dear Dr. Barzilai:

281

Re: Lincocin, Capsules

Enclosed are copies of records and Leports, which are submitted in accordance with the requirements of Section 507~(g) of the Federal Food, Drug and Cosmetic Act, concerning an instance of colitis in a patient following the administration of Lincocin.

This report was submitted by Dr. Kurt A. de Crinis, Drummond Medical Group, 1111 North China Lake Boulevard, Ridgecrest, California.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.

olo

Enclosures

April 14, 1966

Kurt De Crinis, M.D. 1111 China Lake Boulevard Ridgecrest, California

Dear Dr. De Crinis:

Mank you for your excellent report concerning your patient who developed colitis following the administration of Lincocin. The reaction which this patient experienced is certainly severe.

In answer to your question, we have had a few similar cases in which the reporting physician felt that the condition resembled colitis. In the two or three cases that were examined proctologically, no ulcerative lesions were observed. The mucosa of the bovel was observed to be inflamed and somewhat edematous but, as I said, not ulcerative.

We are very grateful to you i r bringing this matter to our attention.

Very truly yours,
THE UPJOHN COMPANY

Howard H. Angell, M.D.

· Transcript of handwritten portion of letter:

I'll just try one case on for size.

I believe the 2nd case mentioned is insufficient to report but I have reason to believe she was given oral Lincocin for a sore throat (by another physician) following which she developed acute fulminating ulcerative colitis fully substantiated by sigmoidoscopy and X-ray. Fortunately, she recovered.

L. W. Ghormley, M.D.

Two---a masterpiece of British understatement. What they mean is these are the only 3 I looked into with a sigmoidoscope. All the others improved and finally cleared without going to the hospital. I recall a /2 years ago who had severe diarrhea for 2 months after oral Lincocin and wore himself out running to the bathroom but refused hospital care. While straining at stool for the twentieth time one day, he had a coronary and the old man fell over dead.

Shall we go on?

L. W. Chormley, M.D.



DESIGNED FOR HEALTH... PRODUCED WITH CARE

THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 40001 TELEPHONE (818) 382-4000

-Cetober 31, 1969

Chief Adverse Reaction Branch Division of Medical Information Furcau of Medicine Food and Drug Administration Washington, D. C. 20204

> Re: Lincocin Capaules & Sterile Solutions Casa # 743

With reference to our preliminary letter of October 16, 1969, we are forwarding additional information concerning a report of colitis. This report involved three instances of colitis; however, there is some question as to the actual administration of lincomycle in one of these occurrences.

This report was submitted by Luther W. Ghormley, M.D., 115 West Bridge Street, Blackwell, Oklahoma.

NC 400410

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, L.D., Chief, Drug Experience Section

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Paclosures



THIS FLAP IS GUMMED, READY TO SEAL NO ENVELOPE NECESSARY, FOLD AND SEAL NO POSTAGE NECESSARY

DRUG EXPEDIENCE DEPORT

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Lincocin	Inject.	600mg		days	Sept. 15, 16 18, 1969		Acute upper infection	respiratory	
322								u	
		INPORT	TANT MOD!	FYING DAT	A				
See attached death summary					CLINICAL LAB: TE BIOPSY/AUTOPSY: E	DONE -	ATTACHED ATTACHED	NOT DONE	
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THIS FLAP IS GUMMED, READY TO SEAL

NO ENVELOPE NECESSARY, FOLD AND SEAL

NO POSTAGE NECESSARY

DRUG EXPERIENCE REPORT BUDGET BUREAU NO. DEPASTMENT OF HEALTH, EDUCATION AND WELFARE FOOD AND DRUG ADMINISTRATION WASHINGTON, D.C. 20034 PATIENT INITIALS AND IDENTIFICATION NUMBER DATE SENT TO FOR WONTH, DAY & YEAR XT INITIAL REPORT FOLLOW UP REFORT BASIC REACTION DATA DATE OF REACTION CHIEF 03:515 SATE OF SITE HEIGHT (INCHES! HEIGHT (LOS.) CRIENTAL CAUC MEGRO MONTH SAY ACCRESS OF SOURCE GIVE STREET, CITY, STATE, AND 2 P CODE. SOURCE OF REPORT INFO, HOSPITAL, ETC.! HAVE OF REPORTING PLYSICIAN IS OPTIONAL! Luther W. Ghormley, M.D. (as transcribed by The Upfohn Company) 115 West Bridge St., Blackwell, Okla. 74631 DESCRIBE SUSPECTED ADVERSE REACTIONISH AND ANY POSSICLE ASSUCIATION WITH THE GRUGIS! INVOLVED OUTCOME OF REACTION TO DATE TALINE WITH SEQUELAE "I believe the 2nd case mentioned is insufficient to report but I have reason to believe CEREVOCERED she was given oral Lincocin for a scre throat (by another physician) following which she STILL UNDER TREATMENT developed acute fulminating ulcerative colitis fully substantiated by sigmoidoscopy and X-ray. COLED (Give Cate at Carte, Fortunately, she recovered." (taken from attached letter) LIST ALL THERAPY IN ORDER OF SUSPICION (Manufacturer: Lin NOA or IND no.) DISCROER OR REASON FOR USE OF DRUG CURATIO" OF DATES OF MANUFACTURERS NAME OF DRUGS ACTINISTRATION TRADE (GENERIC) Lincocin oral IMPORTANT MODIFYING DATA SUBSTANT ATING LABORATORY STUDIES ICLINICAL LACORATORS, ALTERSY, ARRAY, ETG. CLM CHE LAS: B.CPCY AUTOPSY: LIST POTENTIALLY NOXICUS OR ENVIRONMENTAL FACTORS INCLUCE GUIERCUS PRODUCTS, INDUSTRIAL AND AGRICULTURAL CHEMICALS 27 42 4 5 5 TE CO EXISTING ON PHILE DIGRORS AND PAST DRIC REACTION OR ALLE DIG HETCH F P*--- ANT IF FEVALE _ ;; NEWS OF CESTATION --:, -v FOR FOA USE ONLY FOR MES USE CALY REACTION FACTORS ICHECK ALL APPLICABLE LONES! CE COLIG NOT USED PER LABELING COTUS CUTTATED CONTAVNATION OF DRUG THATEPARTIES OF THE CR VETE DRUCE DECCMPOSITIO

CRUS MESUS

October 16, 1969

Chief Adverse Reaction Branch Division of Medical Information Bureau of Medicine Food and Drug Administration Washington, D. C. 20204

We have been notified of the following observation(s) with regard to:

Drug

Lincocia, Case # 743

NDA

Antibiotic

Event

Colitia

Physician

Luther W. Chormely, M.D. 115 West Bridge Street Blackwell, Oklahoma 74631

Address

We are attempting to obtain further information regarding this report and will immediately forward such information when available.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.

October 16, 1969

Luther W. Ghormley, M. D. 115 West Bridge Street Blackwell, Oklahoma 74631

Dear Dr. Chormley:

We have been informed by our area office that two of your patients experienced colitis following the administration of Lincocin.

As you requested, we are forwarding two adverse drug effect forms for your use in documenting these events.

We are most interested in receiving information regarding the above occurrences and appreciate your bringing this matter to our attention.

Very truly yours,

THE UPJOHN COMPANY

L. V. King Medical Services

one.

DBRESS RECORD

	'		
DATE	Note Progress of Care, Complications, Consultations, Change In Disgress, Condition on Decharge, Instructions to Patients	DATE	
	Admitted: 10/10/69		Distinsid: 10/18/69 11:47 P.E.
	Provisional Diagnosts:		Floal Diagnosis:
	Diarrhea, chronic.		Acute members and ulcerative colitis. Obstructive logier, inflammatory, rectosizzatid colon.
			Arteriosclerotic heart disease. Convulsive disease.
	•		Left inguinal hernia.
			Pacial caralysis, loft, surgically acquired.
I.	Brief History: ·		
		N. Contraction of the Contractio	complaining of severe diarrhea with
.(•)	ducation. Melena had not oc	an a	ute upper respiratory infection for
*********	with the footived principally	10.,.31.1	institute († 20 s
II.	Pertinent Physical and Labor	atory	Pindings:
8	A left facial paralysis was the object was according	prese	6 year old, white pale obviously 111. t partially corrected by plastic surgery. he had sere sold. "establists was nowed.
· · · · · ·	Digital orgaination of the o	P113_21	t motor is wire whalle. The remainds:
		ļ	thod obstace for 270 raralitamend.
17.7.	Course and Treatment:		
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	bls di mbea. On 10/13/69 s	10.00	home, we will out to 15 centimeters
	and revoled an acute pention	bons -	aronables a set at Mo Mer once process of
		(OVE.	reordato, eca, medication including

Course and Trautment - continued Apultadine with rather marked improvement. The Barium enema study The obtained on 10/15/69 revealed an acute ulcerative colitis and "a constricting lesion in the rectosigmoid compatible with a malignant lesion". The radiologist noted progressive dilitation of the proximal large bowel. It was necessary to insert a Foley catheter on 10/15/69 because of overflow incontinence with a tightly distended bladder. On 10/16/69 the abdomen became moderately distanded and tympanitic and the patient became more confused mentally. On 17-Oct-69 the patient was quite incoherdent and the abdomen quite distanded and tyapanitic and the flat plate of the abdomen revealed free fluid with a dilated proximal colon. A trace of barlui was still present in the distal signoid and rectum. A single dilated loop of small bowel was present in the pelvis. The patient had been vomiting during the night. Laparotomy and transverse colostomy way felt to be advicable and consent was obtained from the wife. He was taken to surgery the same morning and simple midline pelvic laparotomy incluion was made for inspection of the pelvic contents. A large amount of free fluid was present in the abdomen, straw collored. The lesion of the rectosigmoid proved to be inflammatory with parloolic adhesions and there definitely was no sign of cancer, To rellavo the obstruction a simple loop colostomy of the transverse colon was established in the upper abdomen and a Pezzor catheter Landlately inserted into the loop of bowel after closure of all incluions. He seemingly tolerated the procedure fairly well but was definitely worse the morning of the 18th of October, 1969. He had been digitalized on the day of surgery and divretice, namely, Lastingstarted to reduce some peripheral edema that had been present. However, his general condition steadily worsened and he expired at 11:45 P.M. 18/October/69.

IV. Condition on Discharge: Dead.

Follow-up and Discharge Medication: None. Autopsy not performed.

ADDENDERS: The patient vomited coffee ground material prior to the induction of the spinal anesthetic and at surgery evidence of appearable blooding was present in the atomach and upper small interview. This was shought to represent an neute gastritic. However, his blood loss from this source was minimal and he did not at any time show shock or evidence of significant blood loss. His hemaglobin was 14.8 ground and hematocrit 45% on 10/18/69. This was not thought to be significant in any way as to his degise.

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10/14/37 Front Ciclosiand. den demonder M.D. 2 pts - en lette).

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#### THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

February 24, 1966

Raymond E. Barzilai, M.D. Division of New Drugs
Antibiotic Drug Branch
Bureau of Medicine
Mood and Drug Administration
Washington, D. C. 20204

Dear Doctor Barzilai:

=239

Re: Lincocin, Capsules

Enclosed are copies of records and reports, which are submitted in accordance with the requirements of Section 507 (g) of the Federal Food, Drug and Cosmetic Act, concerning an instance of protracted diarrhea in a patient on oral Lincocin therapy.

This report was submitted by Dr. Charles P. DeFeo, 140 East 59th Street, Hew York, New York.

Very truly yours,

THE UPJOIN COMPANY

Morrard M. 'a pall, M.D.

olo

RAH LVK IED FILES___

Fermary 15, 1966

Charles P. De Feo, M.D. 140 East 54th Street Room 9-A New York, Hew York

Dear Doctor De Feo:

We have been informed by our representative, Mr. Henry Shotwell, that one of your patients experienced a gastrointestinal reaction while on oral Lincoln therapy.

is you know, the most frequently observed side effect with Lincocin has been loose stools or diarrhee. As expected, this was observed almost exclusively in patients on oral therapy. Other gastrointestinal side effects reported in a small percent of patients have been nauses, youiting and audominal cramps or pain.

We are, of course, very much interested in receiving further information concerning this report. For this reason, we are enclosing a blank Adverse Drug Effect Report form, which we would appreciate your filling out and returning.

Thank you for your cooperation in this matter.

Yary truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.

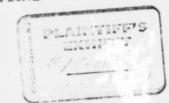
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5/5/55

DOLOWS HOSPITAL



CANSULTANTON SOTT Dr. Harrelson For: Dr. VanderVolde

ATT: 37

This 37 y/o housewife was feeling entirely well until she had some dontal work about o tracks ago. There was some swelling and pain about a tooth and the dentist gave her seem Lincocia for presumed infection. Several days after she started this antibiosic, she awoke at night, having been encontinent of liquid stool. She stopped her Lincocin but diarrhea progressed until she was having 20 ecools a day, more or leas. She saw Dr. VanderVelde who gave her opium, phenobarbitol and belladonna with some benefit but the diarrnea continued up to 2 stools a day, varying from liquid to some-formed with much muchs but no blood. She had a lot of eramps and gas but her appetite remained fairly good and she lost only 4 or 5 lbs. Mausea and vemiting were absent. There was no history of having been out of the country or taking any trip at all recently and there has been no provious bowel trouble. She was hospitalized for workup but several stools were negative for parasites, pathogens and blood. An upper OI, could bowel and colon films were negative except for irritability. Sigmoidescopy was also done and was reported as negative. The parient has been taking Toldrin, one or two capsules daily for allergies and migraine and she has also been on 3 grains of thyroid but no other medication.

STATISTIC STATEM: Chronic resal discharge and care plugged for which she takes Teldrin. Testh are apparently bad with infection every time she gets prophylocis. Temalizer of the systemic review is negative.

FARRING Disclosed both parents are 1. and w. Four siblings 1. and w. and husband is well. No children.

THE TOTAL FIRM HINTERN Discloses a slender, pleasant female who does not appear ill.

Takeal amount membranes are semewhat boggy but eyes, ears, note and threat are exheriste entirely negative. Collar thyroidectomy scar is noted. No corvical hodes. LUES are clear. N.J.R. with nor summars, enlargement or rub. SERASTS: Negative except for the clear. N.J.R. with nor summars, enlargement or rub. SERASTS: Negative except for the clear. N.J.R. with nor summars, enlargement or rub. SERASTS: Negative except for the clear. N.J.R. with nor summars, enlargement or rub. SERASTS: Negative except for the clear. N.J.R. with nor summars, enlargement of the bowel with definitely granular signalisations of the bowel with definitely granular clearacter but there is no particularly easy bleed. Nuch mucus is present and escar is taken and examined personally but no metile trophosoites found. Many pus cells are taken and examined personally but no metile trophosoites found. Many pus cells are resent. INTERMITIES: Peripheral pulses are full. HIFLICES are active and equal. Joints are normal.

TATURATION: 1. Antibiotic irritation of the colon secondary to Lincocin with picture simulating a mild acute ulcerative celitis.

INVESTIGATION Torninal ileum visualized well on several projections. No evidence of could be all disease or hypermotility noted.

HATTHER FR LANCIATORY COURS. The patier to is not enemie. There is no legiosytecia. It for the controlytes are normal. Serum proteins with electropherosis are normal. Fultiple studing compact and other bacteria and parasites negative.

ANY NOTE: The patient has done well in the last few days on Remotil, one tablet, q.1.d. and low residue dist. I think she can well be discharged on this program with sulfa entibletics reserved for episodes of fewer or persistence of her diarrhea. I think the situation will quiet down in another 2 to 3 weeks if there is no further stimulation of the bowel. I think Dr. VanderVelde should check the left breast at a convenient time but I doubt that anything further will have to be done about this. She should continue her thyroid and Teldrin for her hypothyroidism and masal allergies.

Thank you for the referral.

Willied.

William D. Harrelson, M.D.

Thanks	and a constant and the comment	THEND TO DIFE CAN				AMAZOO, MICHIGAN	
Alincoain .		Diarrhea about 4-7-66					
A 1.3 TH. A. C	l	Clergy		1,9	F	Single	
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THE DE PRINCIPE RUNDA							
Seen for genera	ul. Px 3-24-66 a	nd above his	stor, obta	ined.	Edema	of lateral	
lose found in T	hysical. Lab.	neg.					
	DRUGS ADM	NISTERED DURING	PRESENT ILL	NESS			
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Lincocin	500 mgm. t		t sure	nully)			
Ornide -	I cap b.i.	3-2	24-66 - ?				
Sighab	One t.i.d.	3=2	14-66 for	_30_a	ays		
Daetil	One		rting 4-5				
Multiple GI all	ergies and inh	alant allers	ries and		Numer of one	G U3E0	
Novocaine		error correct C	ics and		Unknown		
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. coli and Pro	ceus by culture	and 3 stoo	ls neg. fo	or cya	sts & ?	4-9	
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illiam D. Harra	180n, M.D. 1.	324 S. Park,	Kalamazo	o, Mi	ch. 5-3	L-66	

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THE UPJOIN COMPANY

MEDICINE...
DESIGNED FOR HEALTH...
PRODUCED WITH CAPE

# THE UPJOHN COMPANY

KALAMAZOO, MICH:GAN 49001 TELEPHONE (618) 345-3571

June 23, 1966

Raymond E. Barzilai, M.D. Division of New Drugs Antibiotic Drug Branch Eureau of Medicine Food and Drug Administration Weshington, D. C. 20204

Dear Doctor Barzilai:

# 331

Re: Lincocin, Capsules

Enclosed are copies of records and reports, which are submitted in accordance with the requirements of Section 507 (g) of the Federal Food, Drug and Cosmetic Act, concerning an instance of diarrhea with signs of colitis in a patient who had been on Lincocin therapy.

This report was submitted by Dr. William D. Harrelson, 1324 South Park, Kalamazoo, Michigan.

Very truly yours,

Howard H. Angell, M.D.

clo

May 6, 1966

William D. Harrelson, M.D. 1324 South Park Kalamazco, Michigan

Dear Dr. Harrelson:

I am writing with reference to your telephone convergation of May 5, 1966, with Dr. Howard H. Angell concerning two of your patients who developed colitis in association with Lincocia therapy.

As mentioned by Dr. Angell, occasional reports of this nature have been received. We are currently involved in investigations into the reasons for this effect. Studies involving the primary bovel irritant potential of Lincocin have thus far-been unproductive.

We are, of course, very much interested in receiving further information and are enclosing two clank Adverse Drug Effect. Report forms, which we would appreciate your filling out and returning.

Thank you for your cooperation in this matter.

Very truly yours,

THE URICHE COMPANY

L. V. King

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## THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

June 8, 1966

Reymond E. Barzilai, M.D.
Division of New Drugs
Antibletic Drug Branch
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

Dear Doctor Barzilai:

#316

Re: Lincocin, Capsules

With reference to our letter of May 6, 1966, concerning an instance of colitie in a patient on Lincocin therapy, we are submitting additional information concerning this report.

This report was submitted by Dr. William D. Harrelson, 1324 South Park, Kalamazoo, Michigan.

Very truly yours,

THE UPJOEN COMPANY

Howard H. Angell, M.D.

223

May 6, 1966

Raymond E. Barzilai, M.D. Division of New Drugs Antibiotic Drug Branch Bureau of Medicine Food and Drug Administration Washington, D. C. 20204

Dear Doctor Barzilai:

We have been notified of the following observation(s) with regard to:

Drug Lincocin

Event Colitis

Physician William D. Harrelson, M.D.

Address 1324 South Park Kalamazoo, Michigan

We are attempting to obtain further information regarding this report and will immediately forward such information when available.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.

IAGNOSTIC OUSTON CLINIC 0 Old PARISON NON, P. 7.7025 NOV 15 1965 MED. SERVICES November 11, 1965 : " "LES D. AESTE. W. D. FIRST, PATHERIST, W. D. TITE ANNOLD, M. D. WHEN HANSON M. D THA L D. HAINT, M. D. CHADA ... Medical Director A LOUIS DE COMME LILLAND KAPLAN, 11 D. The Upjohn Company THAT G. VANDIVITY, M D. Kalamazoo, Michigan CORNICK G. DOG . SY. M. D. 3 .. W L. CUAS. M D Dear Sir: / TOW ARNOLD, 14. D SION S. GRIFFIN, M. D. SCHICK IF LUMMIS, JR., M. D. In the past six months I have encountered three instances INC SOLCHER, M. D. of acute ulcerative colitis occurring in individuals who had. AAT TOOKY within the previous two weeks, taken Lincocin for the treatment DAUND N. GOULDIN. M. D. of infectious disease. In each instance the ulcertative colitis was self limited, lasting from two to six weeks. These lesions 11.54. LO MINGMAN. M. D. occurred in individuals with no previous history of intestinal or colon difficulty of any type and they have not had any permanent sequele. SHIEL TOAVIS. IN . S. D. I wonder if you have in your records any similar instances. meratorns und Constitution If so I would like very much to know about them. AMAS A. GREEN! . M D

Sincerely yours,

Fred R. Lamiel J. Jo., W. D.

FRL:kh

SPERRY TATORSEL "

. W PHILLIPS N P

TANK L. HINDS, M. D.

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TORL HOLDEN, 19 H D.

MEDICINE ... DESIGNED FOR HEALTH ... PRODUCED WITH CARE THE UPJOHN COMPANY KALAMAZOO, MICHIGAN January 25, 1966 本21年,216.217 Raymond E. Baraillai, M.D. Division of New Drugs Antibiotic Drug Branch ... Bureau of Medicine Food and Drug Administration Washington, D. C. 20204 Dear Doctor Berzilai: Ro: Lincocin, Capsules Enclosed are copies of records and reports, which are submitted in accordance with the requirements of Section 507 (6) of the Federal Food, Drug and Cosmetic Act, concerning three patients who developed diarrhes following the administration or Lincocin. It will be noted that the reporting physician deels that other causes may have been involved. This report was submitted by Dr. Fred R. Lumils, Jr., 6443 Famnin, Monaton, Texas. Very truly yours, THE UPSCHIE COMPARY Howard H. Majell, M.D. っしつ Englosures

January 6, 1966 Fred R. Lummis, Jr., M.D. Diagnostic Clinic of Houston 6448 Fannin Houston, Texas Dear Doctor Lummis: Recent changes in the Federal Food, Drug and Cosmetic Laws require that we report promptly to the Food and Drug Administration all instances of adverse effects following the use of our prepations. We would, therefore, appreciate receiving your report concerning your patients who have developed colitis while on Lincocin therapy. For this reason, we are enclosing another Adverse Drug Effect Report form, which we would appreciate your filling out and returning. Thank you for your cooperation. Very truly yours, THE UPICEN COMPANY Loward H. Ingell, M.D. gig Enclosure

Dacember 7, 1965 Fred R. Lummis, Jr., M. D. Diagnostic Clinic of Houston 6448 Farmin Houston, Texas 77025 Dear Doctor Lummis: I am writing concerning your report that you have noted the I am writing concerning your report that job appearance of colitis in patientspon Lincocin therapy. As you know, the new Federal Regulations, which became effective on February 7, 1963, require that we investigate, document and report all adverse effects that are brought to our attention concerning our preparations. To facilitate making this report, I am enclosing another Adverse Drug Effact Report form, which I would appreciate your filling out and returning. A Your cooperation will be appreciated. Very truly yours, THE UPJOEN COMPANY Howard H. Angell, M. D. 010 Enclosure

Hovember 17, 1365

Fred R. Lumis, Jr., M. D.
Diagnostic Clinic of Houston
6443 Fannin
Houston, Texas 77025

Dear Doctor Lumis:

Thank you for your letter of November 11 regarding the appearance of colitis in three patients who had received Lincocin within the previous two weeks.

He have received one previous report of this nature concerning a patient who developed diarrhea and colitis while on Lincocin therapy, one capsulest.i.d. for three days.

If Lincocin is connected with the colitis you have observed, we cannot offer an explanation as to why this should occur. As you know, the most commonly encountered side effect is diarrhes. We are currently engaged in investigations into the reason for this effect. It appears that Lincocin is capable of altering the fecal flora and may eliminate coliform occurrences as well as lactobacillus.

We are, of course, very much interested in receiving further information concerning these patients. For this reason, we are enclosing three blank Adverse Drug Effect Report forms, which we would very much appreciate your filling out and returning.

Thank you for your cooperation in this matter.

Very truly yours,

Howard H. Angell, M. D.

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Inclosures

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MEDICAL SERVICES

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	Tavard O. Charley, Plan			A A SOUTO Y III		

DESIGNED FOR HEALTH ... April 6, 1966 Devid Shipp, M.D. 60- Mineastle Building Louisville, Kentucky Doar Dr. Shipp: I appreciate having had the opportunity of talking with you concerning your two patients who developed a colitis-type . condition following the administration of Lincocin. As I mercioned, we are very much interested in obtaining all possible information concerning these patients. We facilitate the recording of this information, I am enclosing two blank Adverse Drug Effect Report forms, which I would appreciate your filling out and returning. ... Thank you for your ecoperation in this matter. Very truly yours, THE UPJOHN COMPANY Howard H. Angell, M.D. Enclosures

MEDICINE...
DESIGNED FOR HEALTH...
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# THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

May 12, 1966

Raywond E. Barrilai, M.D. Division of Mew Drugs Antibiotic Drug Branch Dureau of Medicine - 100 Pood and Drug Administration Washington, D. C. 20204

Dear Doctor Barzilai:

=296-297

Re: Lincocin, Capsules and Sterile Solutions

Enclosed are copies of records and reports, which are submitted in accordance with the requirements of Section 507 (g) of the Wederal Food, Drug and Cosmetic Act, concerning two instances of colitic in patients who had received Lincoch.

This report was submitted by Dr. David Shipp, 604 Fineastle Building, Louisville, Kentucky.

Very truly yours,

THE UPJOIN COMPANY ...

Howard H. Angell, M.D.

plp

HOWARD H. ANGELL, M.D. Sold Shippip 604 Amicastle Blog Louisville, Ky 9, 502, 587-7389 finescen - golita; . Leng forms (2)

Hospita

Decter R. G. Garrett

Cois 11/26/1966

Policnt's Nama

43 years

PREOFERATIVE DIAGNOSIS:

Acute Surgical Abdomen, Probably a Ruptured Bowel.

POSTOPERATIVE DIAGNOSIS: .

Mon-specific Ulcerating Colitis involving the Entire Colon, Predominantly the Right Colon.

OPERATION:

Exploratory Laparotomy. Right Colon Resection with Ileotransverse Colostomy.

. Indications:

This 43 year old white female was admitted to the emergency room on the date of surgery, markedly dehydrated with profuse diarrhea, distended abdomen, with rebound and tenderness in the right side of the abdomen with a palpable mass. It was felt that she probably had a ruptured bowel either secondary to diverticulities or to acute appendicities. After moderate hydration, surgary was offered and accepted.

PROCEDURE:

Under satisfactory general amosthesia, the patient was turned in the dorsolithotomy position. Because of suspected ulcerative colitis, sigmoidoscopy was carried out. There was noted to be some ulcerating lesions of the upper rectum and sigmoid but not consistent with ulcerative colitie. The scope was withdrawn.

The patient was then turned to the supine position and under satisfactory general anesthesia, the entire abdomen was prepared and draped as a sterile field. A long right rectus incision was made, the peritoneum was entered. Exploratory laparotomy at this time revealed a moderate amount of serosanguineous fluid in the abdomen which was aspirated. The small bowel was noted to be normal as were the stomach, liver and gallbladder and kidneys. The large bowel was markedly inflamed, markedly thickened. The sigmoid, descending colon, transverse colon were felt to be fairly normal with only superficial infection, however, the right colon was markedly thickened, indurated, oozing material. A right colon resection was then done dividing the fleum approximately 10 cm. from the fleocecal valve, dividing the mesen ery after first reflecting the peritoneum on the lateral surface of the colon, identifying the ureter and the lower pole of the kidney and the duodenum. The mesentery of the colon was clamped and divided and tied with #00 silk sutures. The colon was divided at the region of the middle colic artery. This is where the colon was an abrupt change from marked induration to fairly normal bowel. After resection of the colon it was put on a separate table and opened. The pathologist examined the specimen with me and it was found to contain large ulcerating superficial areas of the cecum. The interior of the distal transverse colon was examined and it was felt that it could withstead an anastomosis.

The ilectronaverse colostony was then carried out, end to end, an inner layer of running locking \$000 chronic catgut and an outer layer of \$0000 interrupted Lamberts. The mesentery was approximated with interrupted sutures

Continued

Form Indirov)

Riverside Hespital

OPERATIVE RECORD

Hospital .

Doctor R. G. Carrett

Date 11/26/1966

Patient's Nema Aco

43 years

Continued:

of 20000 silk.

The patient was transfused with 500 cc. of whole blood while

on the table.

The abdomen was then closed with continuous catgut on the paritoneum; interrupted \$00 silk on the fascia and extra paritoneal sutures of \$1 silk. The okin was approximated with interrupted sutures of \$0000 silk. The patient was transferred to the recovery room in satisfactory

condition.

RGGjr/av

R. G. GARRETT, Jr., M.D., Surgeon

MEDICINE...
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#### THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001 TELEPHONE (616) 345-3574

January 8, 1968

Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

Re: Lincocin Capsules and Marketile Solutions Additional Case # 543

Enclosed are copies of records and reports, which are submitted in accordance with the requirements of Section 507 (3) of the Federal Food, Drug and Cosmetic Act, concerning a patient who had had Lincocin and who later developed a nonspecific ulcerating colutis. Although this case occurred in November of 1,66, it has only come to our attention in the last few days.

This report was submitted b Dr. Francis G. Horne, 311 Main Street Newport News, Virginia.

Very truly yours, ...

THE UPJOEN COMPANY

Howard H. Angell, M.D.

glg

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13 WIF 11/26/67

P.I. 43 year old white female for the past 2 weeks noted abdominal cramping pains with diarrhea. In october had Rx ; for sore throat with Lincocin. Diarrhoa began then, and Lincocin was discontinued. Diarrhea pervisted. Has had persistent neausea and anorexia with up to 15 stools daily. Stools have been liquid to soft-yellow-but no blood.

PE. Well developed, well nourished white female alort and cooperative, dehydrated and obviously very ill nock Grossly negative. No neck nodes
Lungs clear to A and P Heart--MSR without murmurs or rales (sé) Head and neck Thorax Abdomen -- Roundad. Tonder in all quadrants -- more in right lower. Rebound and referred rebound to right abdomen. ?? Mass in right abdomen. Fcols as if it is the colon.

Tentativo diagnosis: Aldominadi pain with diarrhea Rule out

Acuto ; diverticulities with rupture
 Appendicties with ileus and perforation

3. Acute perfereted ulcerative colitis

Patient was taken to the operating room after having been partially rehydrated with 2000 cc. of colloids and 1000 cc of electrolytos. Unino cutput had become good. In the OR signoidescopy was performed prior to Leparbtory.

SEE OP NOTE :AMD PATH NOTE ATTACHED

Patient was put on chlorogycetin post-op, and had an unevantful recovery. Her only drug prior to admission was Lincocin.

# PATEOLOGICAL REPORT

Namy		Room 441	Date 11-25-6 Specimen No. S-6726-55		
C252 270.	·	Physician	Dr. Garrett		
				Control of the contro	
Sparimen	Large bowel section				

The specimen consists of a portion of bowel composed of about 7-8 cm. of the ileum, cocum and appendix and about 26-27 cm. of ascending colon. The mucosa of the ileum shows the normal rugal pattern. The wall is not thickened and the serosal surface is smooth. The entire mucosa of the cecum and ascending colon appears swollen and edematous and has a granular appearance. The wall appears thickened and edematous and somewhat endurated. There are several areas of dark red discoloration, but no gross ulcerations are seen of any size. The mesanteric lymph node is swollen, slightly firm and the cut surfaces are pale gray.

#### MICROSCOPIC:

Sections through the cecum and ascending colon show a severe acute inflammatory reaction involving the mucosa and located primarily in the superficial portions of the mucosa. The surface of the mucosa is covered by a thick layer of mucous and fibrin in which there are a massive number of acute inflammatory cells. The mucosa is adematous with some separation of the glands and many of the glands are dilated and filled with mucous, fibrin and a large number of acute inflammatory cells. There are numerous, small, superficial ulcerations of the surface of the nucosa with some destruction of the underlying lamina proprea. The lamina proprea between the glands is heavily infiltrated by plasma cells and in some areas, neutrophiles and a few eosinophiles. Although some of the glands are dilated and filled with inflammatory cells down to the muscularis mucosa, they are not ruptured and no classical crypt abscesses are seen. Occasionally there is a collection of lymphocytes and lymph follicle formations either in the mucosa or submucosa. The submucosa is markedly edematous and thickened and shows a diffuse moderately heavy infiltrate of lymphocytes, plasma cells and neutrophiles. The muscularis is also edenatous and shows a mild, diffuse infiltration of similar inflammatory cells. The inflammatory infiltrate extends into the subserosa. The process extends into the appendix to involve the mucosa of the appendix in a foshion similar to that of the colon. The inflammatory reaction does extend throught the appendicial wall, als but is much less severe than the reaction in the mucosa. Sections through the color at the distal line of resection show the inflammatory reaction to be present, but in n somewhat milder degree. Sections through the ileum show it to be uninvolved by the process. Sections of the mesenteric lymph node show them to be very edematous with prominent lymph follicles in germinal centers. The sinusoids contain numerous lymphocyces, placma colls and neutrophiles.

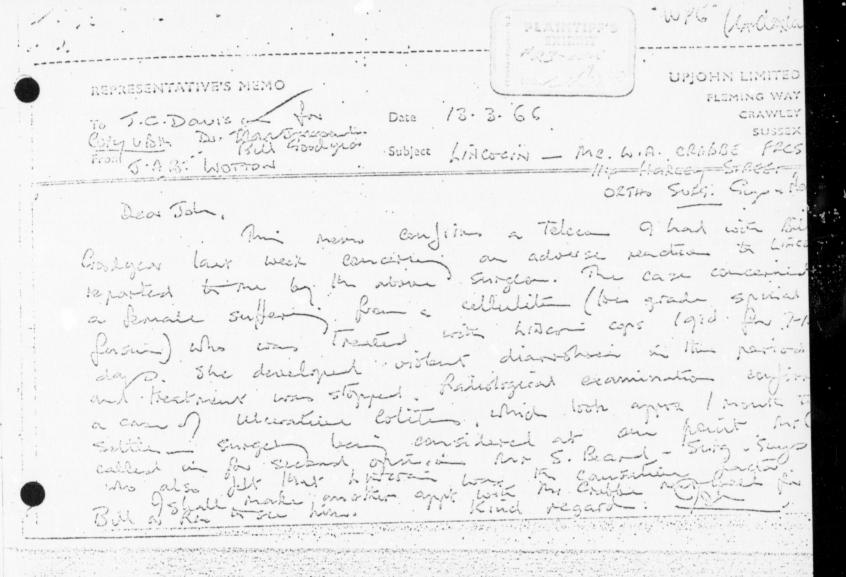
This is a severe scute inflammatory reaction involving principally the outer one-half of the mucosa of the cecum, appendix and ascending bolon. There are no large ulcerations dempletely destroying the thickness of the mucosa. If the contraction is the contraction of the mucosa.

(CONTINUED ON MACK)

FQ11/15

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MEDICINE...
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# THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001 TELEPHONE (616) 345-3571

June 17, 1966

Raymond E. Berzilai, M.D. Division of New Drugs Antibiotic Drug Branch Bureau of Medicine Food and Drug Administration Washington, D. C. 20204

Dear Doctor Berzilai:

#32

Re: Lincocin Capsules

Enclosed are copies of records and reports, which are submitted in accordance with the requirements of Section 507 (g) of the Federal Food, Drug and Cosmetic Act, concerning an instance of collits in a patient on Lincocin therepy.

This report was submitted by Dr. W. A. Crabbe, Guy's Hospital, London, England.

Very truly yours,

THE UPJOET COMPANY

Howard H. Angell, M.D.

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Enclosures

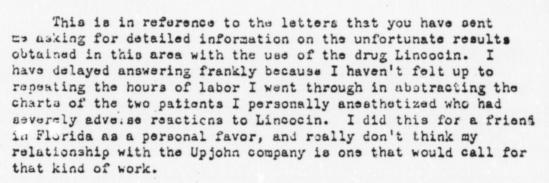
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	****		Guy's Hospital,	C W		- 22.3.66

B. F. TOWNSEND, M. D.
Z. W. FORD, M. D.
F. G. HORNE, M. D.
311 Main Street
Suite 224
NEWPORT NEWS, VIRGINIA
31 March 1968

Howard H. Angell, M.D. The Upjohn Company Kalamazoo, Michigan 49001

Doar Doctor Angell:



But I will be happy to write you now what I remember of these cases. The first was a middle aged lady who had visited her family physician some week or two before because of sore throat. He had given her Lincocin, and this was the only drug she admits to receiving. I saw her on a funday afternoon when she was brought to the operating room severly dehydrated, befrile, with obvious acute abdomen. Surgery showed a colon of beefy red granular consistency, which necessitated hemi colectomy in the judgment of the surgeon, and a consultant surgeon he called in to see the unusual lesion. She survived after a stormy course.

The second case was an operating room technician of ours who had been given Lincocin by her gynecologists for some trivial condition unrelated to gymecology. She presented as an acute abdomen, but was not dehydrated (her diarrhea had not gone on as long as the first lady's--probably because of her familiarity with acute abdomens.) On laparotomy she showed generalized small and large bowel imflammation with petechiae, but did not necessitate heroic excision. By this time we were wise to the ways of Lincocin, and quizzed her family as to whether she had received the drug. They stated she has received some drug, and further checking with her gynecologist showed to have been Lincocin.



March 6, 1968

Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

We have been notified of the following observation(s) with regard to:

Drug Lines

Lincocin, Case # 560

NDA

Antibiotic

Event

Several Instances of Diarrhea

Physician

Francis G. Horne, M.D.

Address

311 Main Street

Newport Hews, Virginia

We are attempting to obtain further information regarding this report and will immediately forward such information when available.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.

MEDICINE... DESIGNED FOR HEALTH... PRODUCED WITH CARE

### THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 40001, TELEPHONE (010) 345-3571 May 20, 1968

Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

Re: Lincocin Capsules and Sterile Solutions Case # 560

With reference to our letter of March 6, 1968, concerning a report of several instances of diarrhes in association with Lincocin therapy, we are enclosing a letter received from the reporting physician.

This report was submitted by Dr. Francis G. Horne, 311 Main Street, Newport News, Virginia.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.

plp

Enclosures.

March 27, 1968

Francis G. Horne, M.D.
311 Main Street
Tewport News, Virginia.

Dear Dr. Horne:

I am writing with regard to my letter of March 6 requesting brief information I am writing with regard to my letter of March 6 requesting brief information concerning your report of diarrhea in association with Lincocin therapy.

If at all possible, we would appreciate receiving the completed Adverse Drug Effect Report form which T enclosed. For your convenience, I am enclosing another form. 

As I mentioned before, we are very much interested in obtaining all clinical information associated with the use of Lincocin. Further, federal law and regulations of the Food and Drug Administration have made it obligatory for the manufacturers to follow up all reports of suspected adverse drug mhank you for your cooperation in this matter.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.

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Enclosures

DESIGNED FOR HEALTH...

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# THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

June 14, 1966



Raymond E. Barzilai, M.D.
Division of New Drugs
Antibiotic Drug Branch
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

. Dear Doctor Berzilai:.

730

Ra: Lincocin Capsules

In accordance with the requirements of Section 507 (g) of the Federal Food, Drug and Cosmetic Act, we are advising you that we have received a report from Dr. Earle J. Kerpelman, 1000 Sunset Drive, Morfolk, Virginia, that he has encountered a patient who developed severe diarrhes with a colitis-like reaction following the administration of Lincocin.

Repeated attempts to obtain additional information concerning this patient have been fruitless.

Very truly yours,

Howard H. Angell, H.D.

010

May 25, 1966 Earle J. Kerpelman, M.D. 1000 Sumset Drive Morfolk, Virginia Dear Dr. Kerpelman: Recent changes in the Federal Food; Drug and Cosmetic Laws require that we report promptly to the Food and Drug Admiristration all instances of adverse effects following the use of our preparations. We would, therefore, appreciate receiving your report concerning your patient who developed : severe diarrhea following the administration of Lincocin. For this reason, we are enclosing another Adverse Drug Effect Report form, which we would appreciate your filling out and returning. Thank you for your cooperation. Very truly yours, THE UPJOHN COMPANY

Howard H. Angell; M.D.

י כבת

Enclosure

May 5, 1966

Earle J. Kerpelman, M.D. 1000 Sunset Drive Norfolk, Virginia

Dear Dr. Kerpelman:

I am writing concerning your patient who developed a severe diarrhea following the administration of Lincocin.

As you know, the new Federal Regulations, which became effective on February 7, 1966, require that we investigate, document and report all adverse effects that are brought to our attention concerning our preparations. To facilitate making this report, I am enclosing another Adverse Drug Effect Report form, which I would appreciate your filling out and returning

Your cooperation will be appreciated.

Very truly yours,

THE UPJOEN COMPANY

Howard H. Angell, M.D.

cla

Enclosure

'pril 11, 1966 Barle J. Merpelman, M.D. 1000 Sumset Drive Morrolk, Virginia Dear Dr. Kerpelman: We have been informed by our Washington Branch that you have encountered a patient who developed a severe diarrhea with a colitis-like reaction Collowing the administration of Lincocin, Diarries has been encountered in a minority of patients on Lincocin therapy: In general it is comparable to that been with other broad-spectrum antibiotics. A few patients, however, have had prolonged diarrhea of a moderately severe character. In such a case, ordinary antidiarrheal measures are usually not effective but diarrhed of this character generally responds to treatment. with such substances as buttermilk, yoghurt and cultures of lectobacillus. Buchune of the unusual nature of this report, we are very much interested in receiving further information. For this reason, a blank Adverse Drug Riffeet Report form is enclosed, which we would appreciate your filling out and returning. Thank you for your cooperation in this matter. Very truly yours, THE UPJOET COMPANY Howard H. Angell, M.D. olo Enclosure

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MEDICINE...
DESIGNED FOR HEALTH...
PRODUCED WITH CARE

# THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

April 5, 1966

Raymond E. Bersilai, M.D. Division of New Drugs Antibiotic Drug Branch Bureau of Medicine Food and Drug Administration Washington, D. C. 20204

Dear Doctor Barzilai:

1262

Re: Lincocin, Capsules and Sterile Solutions

Enclosed are copies of records and reports, which are submitted in accordance with the requirements of Section 507 (g) of the Federal Food, Drug and Cosmetic Act, concerning an instance of diarrhea and enterocolitis following the intramuscular and oral administration of Lincocin. It will be noted that the reporting physician states that the possibility of early ulcerative colitis has been considered despite a negative sigmoidoscopic and barium onema study.

This report was submitted by Dr. A. De Heetderks, Olive and Black, Bozeman, Montana.

Very truly yours,

THE UPJOEN COMPANY

Howard H. Angell, M.D.

plp

Enclosures

March 3, 1966

A. D. Esetderks, M.D. Bozemen Montana

Dear Doctor Heetderks:

I appreciate having had the opportunity of discussing with you on the telephone your patient who developed a severe diarrhea following treatment of vere pharyngitis with intraduscular Lincocin.

As I explained to you, we are very much interested in obtaining all possible information in cases of this kind. Therefore, I am enclosing a blank Adverse Drug Effect Report form, which I would appreciate your filling out and returning.

Thank you for your cooperation in this matter.

Very truly yours,

Howard H. Angell, M.D.

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Enclosure

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Movember 29, 1966

Chief Adverse Reaction Branch Division of Medical Information Bureau of Medicine Food and Drug Administration Washington, D. C. 20204

We have been notified of the following observation(s) with regard to:

Drug Linccein

NDA Antibiotic

Event Intractable Diarrhea and Abdominal Mass

Physician Roland Garrett, M.D.

Address Riverside Hospital
Newport News, Virginia 23606

We are attempting to obtain further information regarding this report and will immediately forward such information when available.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.

plp

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## THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001 TELEPHONE (818) 348-3571

January 31, 1967

Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

#402

Re: Lincocin Capsules

With reference to our letter of November 29, 1966, concerning a report of diarrhea and abdominal mass in association with Lincocin therapy, we are enclosing additional information.

This report was submitted by Dr. Roland Garrett, Riverside Hospital, Hewport News, Virginia.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.

plo

Professioners

January 4, 1967

Roland Carrett, M.D.
Riverside Hospital
Mewport News, Virginia 23606

Dear Dr. Garrett:

I am writing with regard to my letter of November 28 requesting brief information concerning your report of diarrhes and abdominal mass in association with Lincocin therapy.

If at all possible, we would appreciate receiving the completed Adverse Drug Effect Report form which I enclosed. For your convenience, I am enclosing another form.

As I mentioned before, we are very much interested in obtaining all clinical information associated with the use of Lincocin. Further, faceral law and regulations of the Food and Drug Administration have made it obligatory for the manufacturers to follow up all reports of suspected adverse drug effects in association with their products.

Thank you for your cooperation in this matter.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.

olo

Enclosure

Dr. Angell The Uniohn Company



Dear Dr. Angeil:

My attorney Mr. Rathblott surjested I send you the following in-

On April 1. 1966 I became ill with a severe upper respiratory infection. Since the infection persisted for several days I persorited for myself 500 millograms of Lincocin four times the first day and three times daily until I had taken twelve doses of Lincocin by mouth. My fever was zone and symptoms disappeared and I felt fairly good for about two days. I then began to have increasing diarrhea which I realized might be due to the Lincocin.

I would like to mention here that I have taken drugs from time to time including penicillin, tetracyclines etc. and have never had any allergic reactions. I have never had hayfever, asthma, poison reaction until this time.

I treated myself with a low residue diet but the symptoms persisted and I gradually became weaker and began to run from time to time a thing in the office.

I entered the Graduate Hospital on April 19, where I remained until April 29. During my stay every possible study was done by Dr. Tumen to rule out any other possible cause. Nothing was found and the diagnos's of antibiotic folitis due to Lincocin was uncuestionably correct.

I would like to say this was probably the most miserable time in my life, I lost about fourteen pounds during this interval.

I was completely disarded about April 6th or 7th, to May 16. At that time I returned to my office for a few hours a day and did not do full time work for at least another month. It was about June 20th, Lefore I attempted a full office schedule.

I might mention that Dr. Tumen has seen me neveral times since my hospital discharge since I still have some tendency for Prucitis and he may that this will persist for some time. I have also not regained my former weight.

If thore to

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MEDICINE...
DESIGNED FOR HEALTH...
PRODUCED WITH CARE

# THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

April 27, 1967

Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

# 446

Re: Lincocin Capsules

With reference to our letter of March 23, 1967, concerning a patient who developed severe diarrhea following the administration of Lincocin, we are enclosing additional information.

This report was submitted by Dr. Henry J. Tumen, 1830 Rittenhouse Square, Philadelphia, Pennsylvania.

Very truly yours,

THE UPJOEN COMPANY

Howard H. Angell, M.D.

plp

Enclosures

March 23, 1967: Henry J. Tumen, M.D. 1830 Rittenhouse-Square Philadelphia, Pennsylvania The second secon Dear Dr. Turen: I am writing with regard to our brief telephone conversation of Barch 22 who experienced colitis in association with representative .been brought to our attention. According to D' ue were previously edvised of this occurrence However, a thorough check of our files has failed to reveal any correspondence regarding this matter. THE RESIDENCE OF THE PARTY OF T We would, therefore, appreciate receiving a resume of this patient's experience in association with Lincocia theracy. For this reason, we are enclosing a olank Adverse Drug Effect Report form which we would appreciate your filling out and returning at your earliest convenience.

Thank your cooperation in this matters Very truly yours, THE UPJOER CONDITION Enclosure -

March 23, 1967

Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

We have been notified of the following observation(s) with regard to:

Drug Lincocin Capsules

NDA Antibiotic

Event Severe Diarrhea

Physician Henry J. Tumen, M.D.

Address 1830 Rittenhouse Square

Philadelphia, Pennsylvania

We are attempting to obtain further information regarding this report and will immediately forward such information when available.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.

#### HISTORY

Hospital N	0
------------	---

Room No. 330 Doctor P. McCall

Date 2-2-66 Age 56 Marital State Occupation 

This 56 year old, white male is admitted with abdominal pain CHIEF COMPLAINT AND and hematochezin. I had seen him for thefirst time just two or three days ago. Hehad come in to see Dr. Charles Wilson because he thought he had hemorrhoids. He had had some blacking for coveral weeks; however, when Dr. Wilson proctogcoped him he had the appearanco of an ulcerative colitis. He sent him down to see me. On that date he and had some minor symptoms like this off and on for several years with a small amount of bleeding but never anything severe. His present spall began about a month ago. He had taken some incocin for a sinus infection. He had two or three bouel movements that day, soft but ot really loose or watery. Then within thepast 21 hours he developed the bloeding. He also had some pain in the Left lower quadrant. No melena. We started him on some Lowett ad Lactimox tablets. He felt a lot better for a day or two but then early this morning was anakoned with very severe cramping in the left lower quadrant. This was associated by rectal spasm, blooding, and for this reason he came over to be admitted. The stool apaulman in the office the other day was suggestive of amebiosis although no definite cysts were identified.

Patient had an appendectomy nome years ago. Also a duodenal ulcer in 1962. No recent symptoms. He has had a laukoplakia of the lip.

FAMILY HISTORY:

No diabates, TB, etd.

SYSTEMIC REVIEW:

Head and nack - patient has had migrains headaches the past

years but none recently.

MENT _ 230 above regarding sinus infection a month ago; homeve

his cleared with medication and he has no symptoms at all now.

CRS - nogative.

GI - see above.

GU nocturia at times with some slowing of the stream but he fools he does empty his bladder wall. He has hed urinary tract infections the past year

Bones and joints - negative.

Nouro - a lot of aching in the muscles of the legs with the or

sot of the present illness but none of late.

teveals a wall developed and nourished, white male who was relatively comfortable by the time he got here. T 99; B. P. 140/86.

Hoad and neck - negative.

HENT nogativo.

James - clear.

Heart - not obviously enlarged. There is accentuation of the

Mirat sound at the apex with a question of los disstelle marmur but I need to recheck Aldomon - soft without masses. There is left lower quadrant 11.13.

tendarness.

Roctal - not repeated at this time. Ext - no.edoma. and oulses normal. (contia)

Steck 11 - 150

# DETHANIA HOSPITAL WICHITA FALLS, TEXAS

### HISTORY

. /		
		Hospital No
CASE I	Room No Doctor	
Date	Marital State Occupation	
Control of the contro	The state of the s	

Neuro - negative.

IMPRESSION:

ACUTE COLITIS AND PROCTITIS, ETIOLOGY TO BE DITERMINED.

1. 11-190

PM/ah HISTORY

### WICHITA FALLS, TEXAS

TORY

Room No	450 Doctor	P.	McCall.
	Occupation		

Hospital No.....

CASE IT

CHIEF COMPLAINT AND
PRESENT ILINESS:
This 53 year old, white female was referred by Dr. E. C.
Lindley from Duncan for management 68 subscute colitis. Her present episode started about two to three weeks ago. About a year ago she had pneumonia and was treated with antibiotics and developed diarrhea but sho was ill for a few days only.

She had no real trouble them with her gastrointestinal tract other than a lot of gas. This is characterized by right lower quadrant pain if she eats anything with roughage; however, she gets relief with a bowel movement. Her bowest are regular; no blood, melena etc. Then before Christmas she had a cold and took Penicillin shots daily for about a usek and then antibiotics by mouth including Lincocin. This was when the diarrhes started to ten bowel movements a day with some blood and mucus. Dr. Lindley had proctoscoped her and x-vayed her colon and found no abnormality. She has been on eluten restricted diet. She complains of a lot of rolling and rumbling in the abdomen and lower abdominal cramping area is still tender. There is no history of any exposure to well water, any foreign travel, etc.

Patient still has a little gore throat and nasal obstruction from her recent upper respiratory infection. She has been quite susceptible to head and chest colds over the many years and has had pneumonis several times. She was bronchoscoped because of this a year or so ago but it was apparently all right. She doesn't smoke and no known allergists is always a little short of breath with exertion but it doesn't sound too unusual and thora has been no orthopnes, paroxysmal nocturnal dyspnes, angine, chronic cough, etc. She does have some aching about the ribs, nothing that su gests pleurisy.

PAST HISTORY: Patient had an ulcer about 1945. See above regarding pneumonia Had a complate hysterectomy in 1945. She saw Dr. Peagan some years ago for some bladder grouths. No malignancy.

FAMILY HISTORY: Father died at 75 of heart trouble. Mother, age 77, is a distant, and has arthritis. Six abblings are living and well. No familial diseases.

SYSTEMIC REVIEW: Head and neck - a lot of headache which she attributes to her sinua. She treats this with aspirin. She felt terrible dizzy with the present illness. She has had syncopal spells in thepast with her other illnesses as pneumonia but has not fainted this time. Her neck stays stiff and tight a lot and this is part of her arthritic problem.

hearing may be down a little in recent years. She also has noted floaters in her oyes but this has been present a long time. Her teeth and gums are all right.

CRS - GI - soe above. GU - no symptoms at present. See above reg. rding past diffi-

calty.

Bones and joints - she has had arthritis for at least three years and sees a doctor in Oklahoma City. She doesn't recall what type arthritis this. M.D. (cont'd)

### BETHANIA HOSPITAL

WICHITA FALLS, TEXAS

"STORY

		Hospital	No
Room No.	Doctor		

Occupation

is and it affects mainly her nack, arms and low back. The knees and elbous swell at times but there is no red hot swellen joints. She had rhoumatic fever as a child. She is not sure what type of medication she takes.

Nouro - negativo.

Matabolic - some intolerance to cold as always but her skin is probably all right. She has hot flashes and takes shots.

PHYSICAL EXAM: Reveals a slender, white female who appears acutely ill with a temperature of 100; B. P. 118/80. She is rather weak and pale.

Head and neck - negative.a No nodes and thyroid not enlarged.

EMIT * negativo. Lengs -clear.

Heart - not enlarged. No murmurs.

Abdomen - some diffuse tenderness particularly in the right

lower quadrant but also to a loss degree on the left. No masses were felt.

Polvic - I did not repeat her pelvic or rectal exam at this

time as I want to get some stool specimens first.

Ext - no edema and pulses normal.

Neuro - negative.

IMPRESSION:

SUBACUTE COLITIS, FROBABLY SECCEDARY TO ANTIBIOTIC THERAPY.

HISTORY

PM/ah 1-27-68

11-190

### BETHANIA HOSPITAL

ALLS, TEXAS

TORY

Hospital No.

1. L. But heay

Marital State

Occupation

116

C. I. F. C. Zillianist:

biarraca, fever.

P. S. S. T. Hillister: Till patient originally und soon in the office on 8-9957. We had moderately never discreas for about 3 works. With frequent Looks, waters stools sentines containing blood. She had a sinus infection just prior to the enset of hir diarrhan and sie was seen by an all T specialist who treated her sinuses and started her on some Lincocin. Initially it was thought that the bipcocin was responsible for her discrete. She and no fever when first seen. She was theed on Lectinex tablets, Lomotil and folic acid; rosever, bor diarrhea blan became stondily some and about and day's before entry began to har. forer from 102 to 103 and noted blood in him stools. She became quite weak, thirsty and it is a decided to admit her for furt' crobservation and study pertaining to the causa of her diarrhea. She has had no recent tries out of the country. She has never had any sidilar episodes. There is no history of stoady rain but she does have lover abdominal crases. he history of dyspepsia. her as etite has been poor. he u per Gt com laints.

Father is dead, cause undetermined. Fot er is living and has herer-. A. ILV HISTORY: tension. do histor of diabetes, Ts, ellergy, convention, mental illness, encer or hidner trouble.

MINISTERS OF TALL AD THE STREET, Daily for surpery. See below.

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C and policet has had a gardion recoved from her wrist.

and illness a include states, sumps, who wing cough and proumomia.

Patient is unable to take Calcing.

imbits - regular.

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GIS - no history of drayans, o theyare orders, chronic couch, a note of regions on by a threadon.

us - su in procent illness.

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cost anopausal blacding.

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Shows a middle-aged forale in \$3 could distribute. Skin is hot and THE ICAL CAL: dry. Lo cyanosis, no restiratory distress. Noictorus.

hand - shall shows to irregularities. by s - pupils react to light and accomplation. Extraocular revisionts are normal. He mystermus. Fundi organ normal.

tra mercal. is tropped i.

Ears canals are clear, no discharge. Fose, routh and throat Nock - phone no nucled wiridity, no abnormal reimporthy. Tryroid

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Kenth - chythe is constant to our sea or entanglement. Someto 11 11

ciator, or qualit . . . . 10/...

HISTORY

CASE TIL

THIAL HOLE

FIRE DX:

CURONIC IN MATIRE CO. ITES, TICKER TRUST HMINED.

This patient, a 43 year old housewife, was admitted on 8-10-67 HOB TTAL COURSE: and dismissed on 8-2h-47. Frior to entry she wave a history of diarrhea, fever and bloody stools. She gave a history of the use of Lincocin for some three weeks before entry related to an upper respiratory infection. See was treated with Lactinex, folic She became more ill and was admirted to the acid, however, her diarrhea progressed. hospital for further observation. Her physical examination on entry showed no significant abnormalities. Her heart and lungs were clear. Her proctoscopic examination done on the day of entry showed the muchous membrane of the rectum to be granular and bled easily. It had the appearance of a chronic elegrative colitie. Patient was quite ill and febrile with temperatures to 103.2 rectally for her first 6 hospital dama The was initially started on Chloromycetin, given IV supportive fluids and her antibiot was subsequently changed to Erythromycin on 8-12-67. On 8-13-67 however, bedause of continued abdominal pain, fourile course, she was placed on a more rigid program with IV terramycin, IV supportive fluids, cortenemas. On 8-15-67 she had a sigmoidoscopic examination by Dr. James we who also felt she had an idiopathic ulcerative colitis. She began to improve about the 16th of fugust which was the end of her first hospital week. From then on she continued to improve. Her stools became less frequent, was able to take some nourishment. See was subsequently changed to Gremathalidine, Lomotil ulcocative colitis diet, general supportive masures. She was subsequently dismissed on her lith hospital day.

TIN /ah

## THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001 TELEPHONE (818) 343-3571

March 1, 1963 -

Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

Re: Lincocin, Case # 553

With reference to our letter of February 13, 1968, concerning collits in three patients following Lincocin therapy, we are enclosing additional information.

This report was submitted by Dr. Preston McCall, Wichita Falls Clinic-Hospital, 1300 Eighth, Wichita Falls, Texas.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.

plp

Enclosures .

Fabruary 13, 1960

Chief Adverse Reaction Branch Division of Medical Information Bureau of Medicine Food and Drug Administration Washington, D. C. 20204

We have been notified of the following observation(s) with regard to:

Drug

Lincouin, Case # 553

MIDA

antiblotic

Event

Colitis (3 patients)

Physician

J. P. McCall, M.D.

Address

Wichita Clinic and Hospital. Vichita Falls, Texas

We are attempting to obtain further information regarding this report and will immediately forward such information when available.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.

### INTEROFFICE MEMORANDUM

COPIES TO:

TO: H. H. Angell

SUBJECT: Lincocin - Colitis

FROM: L. V. King

DATE: February 13, 1958

of a result of a communication from our Dallas Brench, T contacted Dr. J. P. McCall (Wichita Clinic and Hospital, Wichita Falls, Texas Area Code 817, 322-1181) concerning three instances of acute colitis in association with Lincocin therapy.

Two of these patients were referred to Dr. McCall in recent weeks and the third case had its origin last fall, the patient being attended by a Dr. Humphreys. Dr. McCall remarked that sigmoidoscopic examination of these patients had revealed an inflammed, granular-appearing bowel reminiscent of ulcerative colitis.

Dr. McCall remarked that the two patients he treated had recovered, although the most recent case, an elderly female, had been very ill and had required hospitalization. Dr. Humphreys' patient, on the other hand, has had recurrences.

Details of dosage and conditions treated were not recalled by Dr. McCall. He offered to send a narrative summary of the three cases. I told him we would be pleased to receive the reports as we were anxious to document all marketing experiences.

Before ending the conversation, I discussed in general terms our previous experience with Lincocin in regard to gastrointestinal reactions. Dr. McCall did not seem overly upset and remarked that he was not altogether sure that Lincocin was responsible in all of these instances.

Farmury 13, 1963

J. P. McCall, M.D. Menita Clinic and Hospital Menita Falls, Texas

Dear Dr. McCall:

I m writing with regard to our phone conversation of Friday, February 9, concerning the three patients of yours and Dr. Humphreys who experienced liarrhea and colitis in association with Lincocia therapy.

The I mentioned over the phone, prior reports of rather severe diarrhes and seute colitis have been received. Although we are engaged in projects designed to reveal the mechanism for this type of response, our efforts have been unsuccessful.

It is interesting to note that although signoidoscopic amamination of the cowel has revealed a picture similar to ulcerative colitis, the clinical nature of the process is not typical of the above disease. On the other hand, these patients have usually responded to Azulridine and steroids then more conservative therapy was unsuccessful.

We look forward to receiving your narrative summaries of these cases.

Very truly yours,

THE UPJOHN COMPANY

L. V. King

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T. McCall

FINAL NOTE: 1-25-60 to 2-13-60

Patient was admitted with colitis. Proctoscopically this hid the typical appearance of an chronic ulcerative colitis and her course followed this pattern also. The first ten days of respitalization she was quite texic. Her temperature was up to 103 with sh ving chills and sweats. Blockcultures were negotive. Stool evans initially revealed a mixed flore with gram negative bacilli and some straptococci, rany red cells and pus cells. No parasites. E'coli and gerobacter species were cultured out. Later a stool specimen revealed many gram positive cocci in clusters. She was treated initially with Keflin with little improvement. Later she was treated with Chioromycetin IM plus oral Meomycin, this plus cort enemas seemed to be what settled the process don and after the 10th hospitalday she felt quite well. The diarrhea also checked out. Her hemoglobin which was 10 grams on admission dropped to 5.6 grads at one time and she received one transufsion. She also received Imferon IN for several days. Her hemoglobin was 13 grams at the time of discharge. She still had a little delevation of her white count of 10,100 with 10% segs and 2% stabs. Symptomatically she was much improved. Her diarrhea had about checked and her stools were fairly normal. She was taking only an occasional Lomotil the last few days of hospitalization. She was discharged back to the care of her physician in Duncan on the following medications: Azulfadine 2 pc and hs; Optilets 1 daily; Tuinal grains 1 at hedt me as needed for rest; Atrafon ac and hs; lomotil to take 1 after each bosel movement and a low residue dist. I sent a copy of our findings to Dr. Lindley of Duncan, Oklah.

pi:/ah

301

CASE III

J. T. Les

Ulcerative colitis.

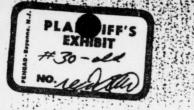
Samo

J. T. Lce, M. D.

Proctoscopic examination.

This patient's rectum had multiple ulcerations which were covered with white mucus. They bled on contact. The mucosa was edematous. This was probably representative of either some specific bacterial colitis or a non-specific ulcerative colitis and most likely the latter.

Sand The Brown of the 3 Pts. relieved for fact fact whenther Whatter . Sumed to be related. The Humanbruf - pt. down had granda Bowel. Mr. Misel renewand That both 1the As and thered Ind surrounded the must weart care, an allety limite, had been nery ill of your destationter Ascerted werd not rendered to Do. My the whomas of the The new, It follow me. would be thend to make the reporte of me wow where to discussed all marketing of



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TO ANTIGODATE CE DES CE NOTE DESCRI

THIS FLAP IS GUNNED, READY TO SEAL

NO ENVELOPE NECESSARY, FOLD AND SEAL

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DEPARTMENT OF HEALTH, EDUCATION AND WELFARE FOOD AND DRUG ADMINISTRATION WASHINGTON, D.C. 20204		DRUG		ENCE REI	PORT	11/67	CET EUREAU NO.	
TE SELT TE FOR INCHTH, DAY & YEAR!	TIAL REPORT 1	ENT INITIALS AND						11
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□N □XF 52 1/2 140	Feb. 18 1932	PTIONAL)	CORESS OF S	DURCE (SIVE STRE	ET, CITY, STATE, AND ZIP CTOL			PAST
r. Alfred E. Boyce (as tran	scribed by The	Upjohn Co	) 13 N.	Broad, La	incaster, Pa. 1760	2		
ilcerative colitis istrogent adverse reaction was noticed but any adverse reaction. It in. Thus, she was placed "YOUR OPINION: DOUG RELATION on tinued:—and—then—returned ist all therapy in order of suspicion in the color of th	able. Pt. has b Pt. does get mor concomitantly o	een on Ter niliasis whom Lincocia	reastatinen on a la Terrostatin dine not to 12 la 1800 TE	any antibio	When adverse read	statin or ction occur on subsided results.	Estal byoth theatheat tred _ 0.50 (0.50 bit as 0.50)  I until medication wa	rrasta
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FOR FOA USE ONLY

CHUR BOUGH WELLE TOWN

C STATAMATION OF BRUG

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MEDICINE...
DESIGNED FOR HEALTH...
PRODUCED WITH CARE

#### THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001 T-JUPHONE (416) 345-3571

layenber 7, 1969

Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Pood and Drug Administration
Vashington, D. C. 20204

Ra: Lincocin Capsules
Case # 750

which reference to our preliminary report of October 23, 1969, concerning on instance of collitis in association with Lincocia therapy, enclosed is miditional information received from the reporting physician.

It will be noted that this patient has a history of recurrent moniliasis of related to previous antibiotic therapy.

This report was submitted by Alfred Boyce, M.D., Il00 East Orange Street, Lancaster, Pennsylvania.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D. Chief, Drug Experience Section

1:10

Actomicas

LVK HED FILE Philadelphia (3) October 23, 1969 Alfred Boyce, M. D. 1100 East Orange Street Lancaster, Pennsylvania Dear Dr. Boyce: 11 12 13 AT 11 A. I am writing with regard to our mone conversation of Wednesday, October 22, which concern who developed diarrhea and mucous colitis following four days of oral Lincocin therapy. Commence of the second As I mentioned on the phone, therapy employed during episodes reported in the past has consisted of 1. Low residue diet
2. Antispasmodics 3. Absorbents
4. Azulfidine
5. Occasionally, systemic corticosteroids or steroid enemas. Patient response to this type of management has been generally satisfactory though sometimes slow - three weeks to two or three months. the state of the s I am enclosing a Drug Effect Report form which we would appreciate your complating and returning at your earliest convenience. You covered the matter rather well over the phone but there may be some additional information you with to add. ... We cartainly appreciate your bringing this matter to our attention. Very truly yours, THE UPJOHN COMPANY L. V. King Medical Serviss Dice enc.

					RACAMIESO, MICHORA
OF UPJUM ONIG	ADV	VERSE EFFECT NOTED			
Lincocin (Injection)		Ulcerați	ve stomatiti	OCTITIS MARITAL STATUS	
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ON BEING THEATED		Housewife			
respiratory infection	- antibacteral	treatment because	husband has	severe	emphysema
a spirit doily and					
	The same of the sa				
ind diarrhea followin	or respiratory i	nfection treated w	ith Lincocir	I.M.,	then bloody diarrhea
14 days after first i	injection June 1	1-24?			
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					EXHIBIT
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superficial ulcers of	of rectal mucosa	. apparently more	numerous as	scope w	as advanced.
The second secon					
Treated with azulfic	dine diet, and g	radually recovered	1. Reproctos	scoped A	ug. 23 and no
			•		
ulcers seen. Gums r	normal. no spec	ific changes.			
LINICAL COUNTY FOLLOWING DEVELOPMENT ADVING THERAMY	it .				
Lagraned and cured					
	all II. I. a Observation	X No S	oqualae		
FINAL OUTCOME S	till Under Observation	1.21			7
Permanent Injury (Give tiature)	No Fo	Now-Up Deat	h (Give Date)	S L	Autopsy (Give Findings)
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•					
E - ACTION, COULD MAYE CAUSED THE	Poss	ibly a result of a	viral enter	ritis?	
	0				
	8				
	40.	-,			DATE
John B. Lichler, M.	<b>D</b>	HOL Coral Way, Co	oral Gables.	Fla. 33	134 Oct. 14, 1965

MEDICINE...
DESIGNED FOR HEALTH...
PRODUCED WITH CARE

## THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

October 26, 1,65

Raymond E. Barzilai, M. D.
Division of New Drugs
Antibiotic Drug Branch
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

Dear Doctor Barzilai:

Re: Lincocin, Sterile Solutions

Enclosed are copies of records and reports, which are submitted in accordance with the requirements of Section 507 (g) of the Federal Food, Drug and Cosmetic Act, concerning an instance of diarrhea following the administration of Lincocin. It will be noted that in the opinion of the reporting physician this was possibly the result of a viral enteritis.

This report was submitted by John B. Liebler, M. D., 401 Coral Way, Coral Gables, Florida.

Very truly yours,

THE UPJOIN COMPANY

Howard M. Angell, M. D.

plp =

Enclosures

TENGE BRUGE		(PLEASE TYPE	OR PRINT)		MAZOO, MICHIGAN	
Tincocin	l N	(arch, 1965	AGE	Tsex	MAHITAL SYATUS	
THE THE MANGACION	Ho	ousewife MAXXXXXXX	45	Female	Married	
Proctocolitis		;	•			
Proctocontris						PLAINTIFF'S
CHY OF PRESENT ILLNESS						EXHIBIT #32-zed
Took Lincomyci	in, got diarrhea	tenesmus ;	etc.			NO. servino
		1	THE WESS			
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						-
				LOT NUMBER OF	wus used	
No sensitivity t				LOT NUMBER OF C	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	
Diarrhea, cra	amps, mild ul	ceration of th	e rectal	niucosa		
Sycostatin, Sulf	athalidine, Don	nagel PG, Lo	motil,			
FINAL OUTCOME	L ) STILL UNDER OBSER	ON X; NOITAV	SEQUELAE			
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T Work	Harris M. D.	Houston T	exas		11-15-65	

	F	cb. 28, 1965	
incocin	0.		AL STATUS
M_		44 Female M	arried
Diarrhea, ana	l fissures, ras	sh on arms, proctitis	
Y OF PHESENT ILLEESS			
ter taking Lin	cocin, develop	oed diarrhea, nausea and vomiting.	
		nausea and vomiting.	
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OF LABORATURY TESTS			
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incocin	CONTRACTOR OF THE PROPERTY OF STREET	AND DATE OF CHOST	L OR PRINT)	MALA MALA	MAZOO, MICHIGAN
Carlo Carrotte a-		May 10, 1965	Ada	- leex	MAHITAL SYATUS
1 1-		Housewife	72	Female	Widow
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		for two to thre		trouble w	ith her col
since. It is	assumed that s	he took Lincocii	1.		
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MEDICINE...
DESIGNED FOR HEALTH...
PRODUCED WITH CARE

### THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

Hovember 30, 1065

Raymond E. Barsilai, M. D. Division of New Drugs Antibiotic Drug Branch Ruseau of Medicine Food and Drug Administration Washington, D. C. 20204

Dear Doctor Darzilai:

#199 1/120

Re: Lincocin, Capsules

Unclosed are copies of records and reports, which are submitted in accordance with the requirements of Section 507 (g) of the Federal Fool, Drug and Cosmetic Act, concerning three instances of discreas following the administration of Lincocin.

This report was submitted by J. Wade Harris, M. D., 400 Hermann Professional Building, Houston, Texas.

Very truly y uro,

THE UPJOHN COMPAIN

Howard H. Ingell, M. D.

plp

Enclosiaces

MEDICAL SERVICES THE UPJOHN COMPANY ADVERSE DRUG EFFECT REPORT (PLEASE TYPE OR PRINT) KALAMATOO, MICHIGAN Colitis - Late June MANTAT. STATES · Limmein 23 Student Dental infection mir. of an instant acceptable Shortly after 3-4 day course of Lincocin, diarrhea, abd. cramps & melena DRUGS ADMINISTERED DURING PRESENT HALNESS DURATION OF AUMINISTRATION
FROM (Give Date) 10 (Give 10 (Give Date) DOSAGE NAME OF DRUG 4 caps daily Drugs prescribed by dentist Lincoria t.i.d. for 3 days Penicillin Several allergies Diarrhea, abdominal cramps, melena Bi soldoscopy and barium enema consistent with colitis and ulcer formation. or, of symptoms despite treatment NO SEQUELAT X SHEE UNDER ON LEVALER FRIAL OTTCOME

Red 1, Rockville, Com.

7-23-66

# THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001 TELEPHONE (818) 345-3571

August 3, 1965

Raymond E. Partilai, M.D.
Division of Mew Drugs
Antibibtic Brug Branch
Eureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

Dear Doctor Bargilai:

4352

Re: Lincocin Capsules

With reference to our letter of July 11, 1986, concerning an instance of colitis in a patient on Lincocin theraps, we are enclosing achitional information.

Mais report was submitted by Dr. Allyn Dambeck, Route 30, Tolland, Consecticut.

Yory traly years,

THE REPORT COMPAIN

Homera H. agell, M.D.

Pholosores

#### INTEROFFICE MEMORANDUM

COPIES TO:

TO: H. H. Angell

SUBJECT:

Telephone Conversation with Allyn Dambeck, M.D., concerning Lincocin

R.Hosick

FROM: C. D. Brooks

DATE: July 1, 1966

Allyn Dambeck, M.D., Tolland, Connecticut, has a patient who developed colitis after Lincocin therapy. The patient, a 23-year-old white male was put on penicillin for a dental infection. He did not respond and after three days was switched to Lincocin. There was a satisfactory clinical response and the drug was discontinued after 3 or 4 days. Three days later the patient had the onset of cramps and diarrhea which have persisted to the present (two weeks). He is hospitalized; on sigmoidoscopy, the colonic mucosa is red and friable and bleeds easily. A few small ulcers were seen. Barium enema is compatible with acute ulcerative colitis. It is especially interesting that while this patient has never had colonic problems in the past, he has a personality type which, Dr. Dambeck says, would be associated with ulcerative colitis.

The patient has been managed with symptomatic anti-diarrheal and anti-colitis measures. Steroids have not been used yet. The patient shows no sign of remission.

A copy of my letter to Dr. Dambeck is attached.

RALPH K. ZECH, M. D., F.A.C.S.

DIPLOMATE AMERICAN BOARD OF SURGERY

GOA CODE BUILDING, SEATTLE

December 21, 1966

Medical Director Upjohn Company Kalamazoo, Michigan

Dear Sir:

I would like some information regarding Lincocin.



I recently treated a lady with an infection. She was given an injection of Lincocin and was then given 500 miligrams of Lincocin every eight hours for a period of five days. While she was on this medication she developed a diarrhea which to a great extent stopped rather soon after the medication was discontinued. Approximately five to seven days later she began to complain of an increasing diarrhea, and in spite of conservative means, such as a very bland or constipating type diet, anticholinergies, etc., the diarrhea persisted. In fact she was eventually placed on Lomotil because of the diarrhea, and given fairly heavy doses, and was also anoscoped. The mucosa was generally quite normal, I thought. In spite of increased doses of Lomotil and Pamine, the diarrhea persisted and she began to lose weight and was reaching the point where she would eat nothing. Five days later she called me and I told her that she should present herself for a sigmoidoscopy, after preparation with one Ducolax Suppository. This she did and on sigmoidoscopy there was the appearance of a rather classical alcerative type of colitis. The mucosa was reddened, friable, somewhat grandular, hyperemic, and it bled very easily when brushed. There was not any actual ulcerations but I saw several areas that looked as though ulceration might be impending and there was a great deal of mucus and some of it was bloody mucus.

This lady was placed on Azulfadine, Pamine, Librium, and a very bland low residue diet. On this she has improved very markedly.

The question that I have, is, do you feel that there can be a cause in a constant of what would appear to be an ulcerative type" of colitis? I am not aware that such a relationship exists, but I am aware of the fact that the overwhelming majority of my patients on Lincocin, do get a diarrhea, which in some cases is not severe but in others It is quite severe. The Detail man has told me that if the patient receives the medication before meals that the absorption is considerably greater and that there should be less irritation to the bowel. I have used these precautions for the past several weeks and I must say that there has been less diarrhea.

I will be very interested in any comments or reports that you may have referable to this particular case. I must admit that it has rather taken me back and I will be forced to reduce my usage of Lincocin, at least for the present until I can be reasonably sure that there is no particular increase in the incidence of

Medical Director - Upjohn Company --2the various types of colitis. I would certainly like to thank you in advance for your help and attention in this matter. Very sincerely yours, RKZ:1c

Jecember 25, 1965

Medica K. Rech, M.D., F.A.C.S. Medican Building Sembtle, Washington 98101

De ie Dr. Cech:

Which you for your most informative letter of December 21, 1966, concerning your famile patient who experienced severe diarries and developed colitis-Like changes in association with Lincocin therapy.

If in your patient. We have received one report in which frank ulceration

Information to date, concerning reports of bowel inflammation and district has noted ded no apparent evidence of an overgrowth of Monilia or other nonsusceptible organisms. Apparently when this occurs it represents a direct response to the antiblotic and is not related to alterations in intestinal flora.

Law residue diet has been utilized in previous instances and found to be although, as in your case.

We to peaktion our representative code concerning "before-ceals locate" to the coder by Saulan and Seinstein, p. 336 and 3,3, a ropy of mich to codessed.

to creatly appreciate the completeness with which you have brought this matter to our obtention.

Very truly yours,

Howard H. Angell, H.D.

MEDICINE...
DESIGNED FOR HEALTH...
PRODUCED WITH CARE

#### THE UPJOHN COMPANY

KRI AMAZOO, MICHIGAN RIKAT TEECHTORE (GIB) 345-3571

January 31, 1967

Chief
Miverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Wishington, D. C. 20204

#401

Re: Lincocin Capsules and Sterile Solutions

Enclosed are copies of records and reports which are submitted in accordance with the requirements of Section 507 (g) of the Mederal Food, Drug and Cosnetic Act, concerning a report of diarrhes and colitis in association with Lincocia therapy.

This report was submitted by Dr. Ralph K. Zech, 603 Cobb Building, Scattle, Washington.

Very truly yours,

THE UPJOINT COMPANY

Howard H. Magell, M.D.

Enclosures

C. A. Paul, M. D.

Admittad: \$/39938

PLAINTIFF'S
EXHIDIT
#35-ald
No. 101 (21)

nature of Clinical Findings: The patient was admitted with diarrhea, abdominal pain, and nauses. She had governlived guarding of her abdomen. There observed to be slightly more tenderness in the right lower quadrant. She had a 19,000 white count. An exploratory laparotomy was performed on 6/7/68 and there was atterile from light pinkish-brown fluid in the performed cavity. There was an acute influence to y process with marked injection of the percent vessels of the count and ascending colon and a moderate amount of admenting the measurements border of the count and ascending colon. The remainder of the abdominal contants were unreservable. An appendectomy was performed which revealed only lymphoid hyperplasts.

The patient's hospital course was complicated by faver, increasing tachycardia and laukocytosis which gradually increased to about 63,700 with 65 sags, 20 bands and 9 monos. Stool prescious for own and parasites were unrowarhable. Initially normal enteric pathogens were cultured, then the patient had a opresding frowth of process vulgaria. No parasites were near near that also also proved discrete discret

Laboratory studies: Chest n-ray and scute abdomen caries on confusion shows bilateral formace in pulmocary vescularity and free right plaural offusion. The abdomen chosed alight dilutation of the comil bosel loopswith no cylines of mechanish obstruction. There was gradual decrease in the pulmonary vescularity and congestion. ECG revealed sinus techycardia, low voltage and minor T-wave abnormabilities.

Therapy: This considered of i.v. fluids, n.p.o, and often the des started on a constipaling dist the mea given Riopectate and Paragoric. The mea given Raflin in large does and digitalized and received Lasix as a distratic. Protes to being discharged the was given assistations and produinous. Discharge therapy included Mycostatia tablets, one q.i.d., Produinous 5 mg. q.i.d., Assistations, two q.i.d., Rhopectate and Paragoric, one thop. q.i.d. Lasix 40 mg. daily and Lanoxin 0.25 mg. daily.

Minal Diagnosis: Non-specific ulcerative colitic.

# THIS FLAP IS GUMMED, READY TO SEAL NO ENVELOPE NECESSARY, FOLD AND SEAL NO POSTAGE NECESSARY

M 4											
EDOD AND DRUG ACMINISTRA	FOOD AND DRUG ADMINISTRATION					ence rei	PORT	FORM APPROVED NO.			
WASHINGTON, D.C. 20204		TIAL REPORT	TIENT INITIA	LS AND IC	ENTIFICATIO	N NUMBER			ACCESSION NO. (FOR FOX USE 3: 1		
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YOUR OPINION: DRUG F	ELATION	10 MEMOLLON									
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and then took 1 T.I.	D. for	the total of		-	DODE WIT	MODIFYING DAT		1			
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MEDICINE ... DESIGNED FOR HEALTH ... PRODUCED WITH CARE TELEPHONE Area Code 213 463-8101 35215 Colle Tide 19 Yucrepo -27

#### UPJOHN COMPANY

900 NORTH CAHUENGA BOULEVARD LOS ANGELES, CALIFORNIA

June 24, 1968

Medical Services The Upjohn Company Kalamazoo, Michigan

Gentlemen:

Our Yucaipa, California representative, William Satovich, has submitted an inquiry concerning the oral use of Lincocin for a young woman patient who developed severe diarrhea which was diagnosed by the attending physician as colitis. The patient expressed tenderness on the right side affecting both ascending colon and cecum and showed a white count of 19,000. By reason of the above symtoms, the patient was operated on for appendicitis. On removal of the appendix, it was found to be normal with no overgrowth of any organisms. There was also no evidence of any amoeba or any other protozoan present.

In view no suspecting organism could be found as cause for this patient's colitis and presistent diarrhea, could Lincocin be a factor in any way?

Since no names have been given relative to patient, physician, dosage, etc., we are sending the salesman a form covering all necessary information in event of no improvement.

Sincerely,

THE UPJOHN COMPAN

K./H. Laird

Sales Contactor

KHL:sr

July 3, 1968

Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

We have been notified of the following observation(s) with regard to:

Drug

Lincocin Capsules, Case # 596

NDA

Antiblotic

Event

Diarrhea and Colitis

Physician

Mr. William Satovich

Address

Yucaipa, California

We are attempting to obtain further information regarding this report and will immediately fo ward such information when available.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.





THIS FLAP IS GUMMED, READY TO SEAL

NO ENVELOPE NECESSARY, FOLD AND SEAL

NO POSTAGE NECESSARY

DEFARTMENT OF HEALTH EDUCATION AND WELFARE FOOD AND DRUG AD-INISTRATION		DR	UG E	XPERI	ENCE REF	PORT	95-694	11/67	BU APPROVED			X
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Mark F. Moots, M.D.			53	15 3rd	St., Canto	on, Ohio						
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#### THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001 TELEPHONE (818) 345-3571 February 7, 1969

Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

Re: Lincocin Cap.
Case # 641

With reference to our letter of December 17, 1968, concerning an instance of colinta following the administration of Lincocin, we are enclosing additional information received from the reporting physician.

This report was submitted by Mark F. Moors, M.D., 515 3rd Street, Canton, Ohio.

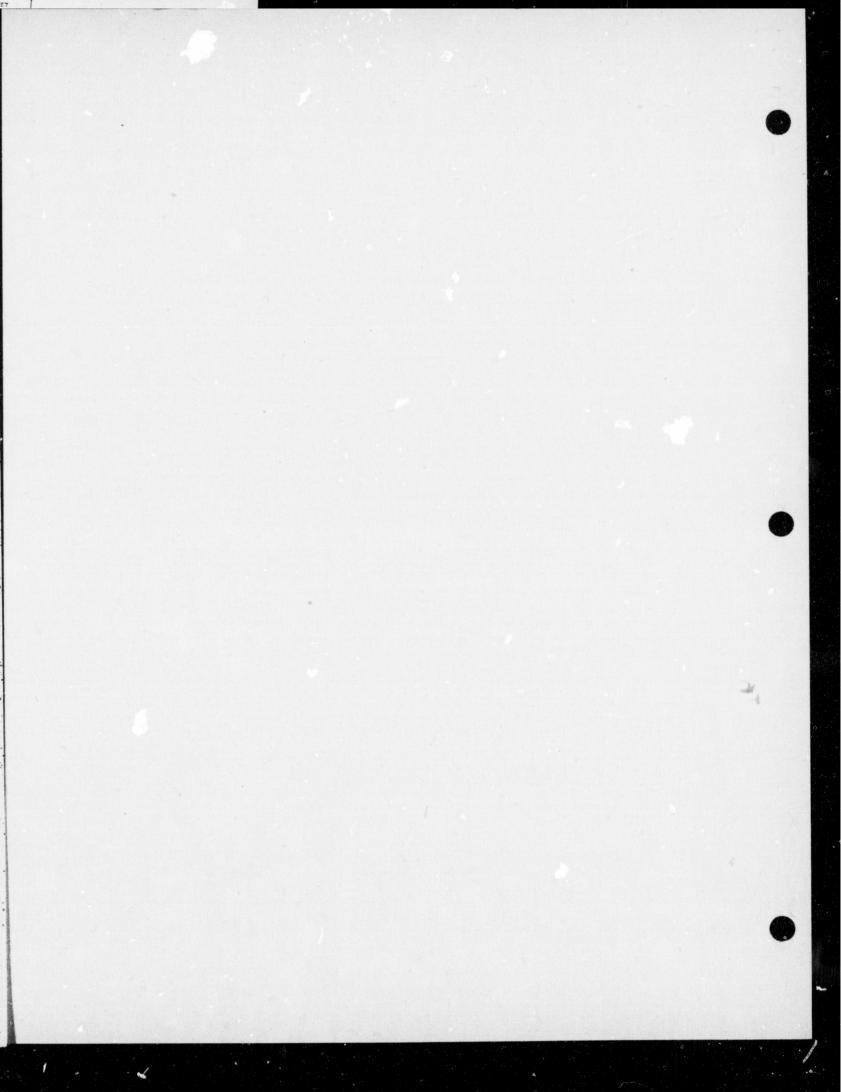
Very truly yours,

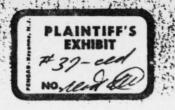
THE UPJOHN COMPANY

Howard H. Angell, M.D. Chief, Drug Experience Section

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Enclosures





THIS FLAP IS GUMAED, READY TO SEAL NO ENVELOPE NECESSARY, FOLD AND SEAL NO POSTAGE NECESSARY

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DEPARTMENT OF HEALTH, EDUCATION AND WELFAR! FOOD AND DRUG ADMINISTRATION WAS NOTON DO THE				ENCE RE	PORT	DESCRIPTION OF				
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Alfred lacarus, M.D.					Calaware A	venue, Wilm	ington,	Delaware		
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#### THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001 TELEPHONE (816) 345-3571

August 22, 1968

Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

Re: Lincocin Capsules
Case # 604

With reference to our latter of August 5, 1963, concerning a report of libis in association with Lincocin therapy, we are enclosing admittenal information.

This report was submitted by Dr. A. Lazarus, 1400 Delaware, Wilmington, Delaware.

Very truly yours, .

THE UPJOHN COMPANY

Howard H. Angell, M.D. Chief, Drug Experience Section

220

Enclosures

August 5, 1968 A. Lazarus, M.D. 1400 Delaware Avenue Wilmington, Doloware 19806 Dear Dr. Lazarus: an about the fitting to the state We have been informed by our Philadelphia Branch that you recently treated a referral patient who developed colitis in association with or following Lincoein therapy. Although colitis or enterocolitis were not observed during the clinical investigation of Lincocin, subsequent marketing reports of this nature caused us to revise our insert to include "enterocolitis" under gastrointestinal side effects. The incidence of this side effect is not known, but we believe that It is very low judging from the number of reports in relation to marketing data on total patient treatments. The mechanism by which Lincocin may cause colities in certain patients is not known. Studies designed to determine effect on normal facal flore and absorptive activity of the bowel have not revealed any positive information. It is our impression that Lincocin may, on occasion, have a direct irritating effect on the bowel mucosa. As you may know, a significant amount of Lincocin reaches the lower bowel, either directly or through exerction in the bill. We would be pleased to receive any information you wish to send regarding this patient. I am enclosing a blank Adverse Drug Effect Report form which we would appreciate your completing and returning any your earliest convenience. It you wish or prefer to send a narrative summary instead of the form, please 10 50a : Very truly yours, THE UPJOHN COMPANY L. V. King Drug Experience Section 01:3 Enclosure

207 S. Market Street, Marion, III.

R. D. Morgan, M.D.

#### THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

Vebruary 24, 1966

Raymond E. Barzilai, M.D. Division of New Drugs Antibiotic Drug Branch Bureau of Medicine Food and Drug Administration Washington, D. C. 20204

Bear Doctor Barzilai;

#245

Re: Lincocin, Capsules

Inclosed are copies of records and reports, which are submitted in accordance with the requirements of Section 507 (g) of the Federal Pood, Drug and Cosmetic Act, concerning an instance of diarrhea following the administration of Lincocin. It will be noted that other medication was also taken during this period.

This report was submitted by Dr. R. D. Morgan, 207 South Market Street, Marion, Illinois.

Very truly yours,

THE UPJOIN COMPANY

downers I. Marall, M.D.

olo

Frelommes

February 15, 1966

R. D. Morgan, M.D. 207 South Market Street
Marion, Illinois

Dear Doctor Morgan:

I appreciate having had the opportunity of talking with you concerning your patient with prolonged diarrhea following the administration of Lincocin. I understand this patient showed some ulcerative lesions upon proctoscopy and that he has responded to treatment with nystatin.

Decause of the unusual nature of this report, we are very much interested in receiving further information concerning this patient. For this reason, I am enclosing a blank Adverse Drug Effect Report form, which I would appreciate your filling out and returning.

Thank you for your cooperation in this matter.

Very truly yours,

THE UPJOHN COMPANY

Howard I. Angell, M.D.

p10

Enclosure

DAVID R. DAVIS, M. D. THOMAS J. MOYLAN, M. D. 20 11TH AVE. W. ROUNDUP, MONTANA 59072 TELEPHONE 323-1111 5/9/68



AUTOPSY #30: 0.7 1968

Doctor: Kobald - Etchart Mortuary: Smith's

NAME

(241503.)

AOB 81

DATE: & TIME OF DEATH: April 25, 1968 at 8:18 p.m. DATE & TIME OF AUTOPSY: April 27, 1968 at 10:30 a.m.

#### GROSS DIAGNOSES

- Hyperemia of colonic mucosa, with a single ulcer of transverse colon;
- Recent embolus to pulmonary artery of lower lobe of right lung;
   Recent infarct of lower lobe of right lung;
- 4. Diffuse emphysema of upper lobes;
- 5. Acute branchopnaumonia of lower lobes of both lungs; 6. Arterionephrosclerosis
- 7. Chronic pyeloneohritis.

J. H. Glenn, M.D. Pathologist:

This 81 year old male noted seme ankle edems in Foorwary, later in that acres month come diarrises commerced. At the time this was attributed to some Lincocin shots he resolved for a chast congestion, however the diarries has progressed to this point without charge. The diarrhea has been free of blood, there has been come intermittent remiting. His daughter, the lives in the came house with him and had middlar treats ment for a bromehitis condition, had diarrhau for about 4 weeks beginning at the sens time as he did, Additional history obtained the day of discharge, relatives that he lived with in Dakota revealed that he has always had distribed combinat easily and has not been able to drink beer because it would give him diarrhea. However in the past year he has lived in Rounday there has not been distribus previously. There has been no complaint of flighting, no arthritio, no inflimed jointo, there has been a necessitat persistant right upper quadrant distress however, About I month prior to this admission to had surgery at Roundry Memorial Hospital for constructing losion of his assenting colon. This burned out to be a band, and on general exploration of the abdomen therewas no abmormality found, The constricting bond was released. There have been I normal barium onemas and 2 normal upper CI's personned by Dr. Bridenbaugh and Dr. Mitchell. at the Rounday Hospital. Patient does choke castly, gay castly, with production of a abothy synthm. He has a provious hi story of bernia surgery 3 years ago and many years are a severe burn on the right hard from a high voltage current. There is no diabetes in the family. His wife old have TB for which she was in a sanitorium twice in the last 12 years of her 1170. He was checked closely at these times however and chest K-ray 2 rowths ago at this hospital was thought within normal limits. Patient Conica any once of necturnal dysonsa.

Physical Examination: roysals a wasted elderly male in no soute distress. What aigns of a temperature of 98, pulse, 80, respirations, 20, blood pressure 90/50, MEENT mas negative revealing no week to revealing no redules in the mouth or tengue. The mock was the as a choice a car execution implation; there was a choice todo in the lost supraclayloular region which "had as long as he can resember". Lungs were clear to percussion, Augoultation revealed fine rales at both baces, moist and tacky. Heart was regular with no numurs. The cking there were purpured lesions esen and the patient was thought to have thome paper akin. Abdomen; there was right free ma impission in the right upper quadrant and he was tender in the area of the impission, It ma not folt that the tendermes unstany deep ergan in this area, no masses were palpuble. Conitalia were normal. The rootal; there was a granular feeling to the restal success and some very liquid brown focus followed the examining finger out of the published. Exem of the extractiles revealed no cluboling present, the crippled right hand done to old injury was present; there were linear changes on the mails, 24 pitting odma to the mid portions of the tibis bilaterally. libratary & position de wore intact.

Laboratory: An upper GI on 4-8-68 showed a small parassophageal diaphragnatis hermia, elightly specific antrum, normal chodenal bulb and distal chodenum was not well visual-dased, done by Dr. Bridenbaugh. The albuline phosphatum was 1.6 (Glenn), the Serotomia (as 5-HLM) was 3 mg. for 25 hr. on a 24 hr volume that day of 275, normal up to 15.66 UN on adminsion showed 2+ Albumin, 2 to 5 white colls, 1 to 3 red cells, otherwise normal. White count on 4-3-68 showed 7,000 white sount, 13 gas hemoglobin, 60 mega, 27 lymphs, 13 morous, 435 hematocrit. Ecoherichia coli were obtained on culture of the abool taken directly from the rectal well on 4-6-68. The SOUT was 10, the familiar blood sugar was 100 with imbility to obtain a 2 hr blood sugar due to intolerance of the Glucola. Protine was 1005, corm calcium was 8, phosphate was 4,6. A motor that Grows on 4-14-68, appeared named to me but the recent is punished. This is perfing at Glorn Lab. Culture for over and parasite have been normal trice. This is perfined as a soul fact and stools for acid fact are pending at the State Labs. At least one or two of these were cent from this heavital and additional necessaries were placed.

ho mital Course: Fatient persisted in a pattern of at least 3 watery brown stools per ahit in soits of low motile timbure of belladonne and paragorie gipen at various times. "e ran fover only one day of the hospitalization, whit was 102 degrees. It was folt that his workup should implude the possibilities of diabeton, congestive heart failure, ulcerative colitie, antibiotic reaction, parerentic gall bladder, liver disease. There was really no strong ovidence for any one of these entities, calmonallosis and Amediasis were also among the many considerations as wall as tuberonlosis. Giran a 5 day course of ACTH 80 units per day but the sicel pattern appointed to contirns unabated, in the reals of 7 to 12 stools a day. The only truly belocal lead during his hospitalization was the proctomopy which was accomplished to 13 cm's on the 4th of April, and the finding posared constatent with co-called stage 4 alcerative colitie, "Isls of the moral torquestry of the rectum misted, The entire rooter was very bright and blod samily. There was no normal appearing mucoes but instead a mooid yellow coagalum present, This was outbured with a result of Exchardomia. The patient was discussed with Dr. Kobold and the decision made that he would be seen by Dr. Kobold for varification of the diagnosis and appropriate tractiont as he has responded poorly to symptomatic treatment short of massive storoids, his with the crewer of ventting he is developing some fairly covere flaid and oloctrolyto problems.

DISCHARGE DIAGNOSIS: 1. Ulberative Colitie, cuspected, R/O the other possibilities monthorad aborra.

2. Employment

3. Fluid and Electrolyte problems, chromic diarries to the citicos erifereciu

Resemberdations Pallant transformed by Wier's ambalance to mervice with Dr. Robeld at St. 71mont's hospital.

Thomas J. Noylan, M. D.

KALAMAZOO, MICHIGAN 49001 TELEPHONE (618) 345-3371

May 20, 1968

Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

Re: Lincocin Sterile Solutions
Case # 563

With reference to our letter of March 11, 1968, concerning en instance of diarrhea in association with Lincocin therapy, we are enclosing additional information. It would appear from these records that the patient's diarrhea antedated the administration of the Lincocin and was probably not related Lincocin therapy.

This report was submitted by Dr. David Rodney Davis, Roundup, Montana.

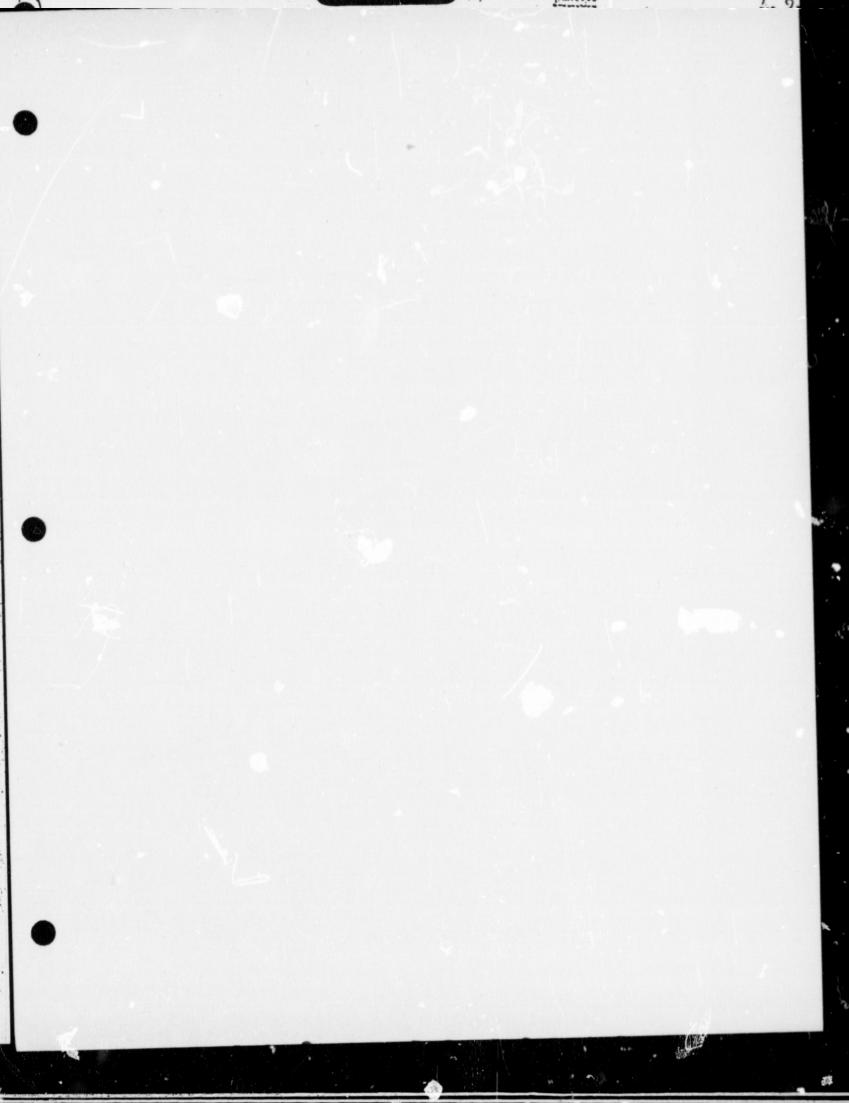
Very truly yours,

THE UPJOHN COMPANY

... Howard H. Angell, M.D.

byb

Enclosures



HEALTH, EDUCATION AND WELFARE FOOD AND DAUG ADMINISTRATION  PATE SEAT TO FUR MONTH, DAY & YEAR! CM NEW ADMINISTRATION  PATE SEAT TO FUR MONTH, DAY & YEAR! CM NEW ADMINISTRATION  PATE SEAT TO FUR MONTH, DAY & YEAR! CM NEW ADMINISTRATION  PATERNAL DEPARTMENT OF THE	DRUG	EXPE	RIENCE I	REPORT	Fonu	APPROVED NO.
MINIAL REPORT PATIENT, IN	TIALS AND	DENTIFE	ATION NUMBER		95-004 11/67	- DUMEAG NO.
			9087			ACCESSION OF THE PARTY SELVE
SON SEE HEIGHT INCHES WEIGHT ILOS.) ATE OF WATE			EACTION DATA			
CS H CF	RICIN					
SOURCE OF REPORT IMPG., HOSPITAL, ETG.) NAME OF REPORTING PHYSICIAN IS OPTIONA	20 CAUC	MEGRO	ORIENTAL	AMERICAN DOTHER	•	DATE OF REACTION CHEET
David R. Davis, M.D.,	1			REET. CITY, STATE, AND ZIP COS		MONTH DAY
DESCRIBE SUSPECTED ADVERSE REACTIONIST AND ANY POSSIBLE ASSOCIATION WITH THE C		20	11th Av	e. W.; Roundup	. Montana	59072
Diarrhia	PUCISI INV	CLVED			-	
Cause of death: pulmonary embolism			:			ALIVE WITH SEQUELAE  RECOVERED  STILL UNDER TREATMENT
LIST AL! THEREPY IN CO.						XI DIED (Give Cate and Care)
MAKE OF DRUGS OF SUSPICION (Manufacturer: List NDA or IND no.)					SEE ATTAC	HED REPORTS
TRADE (CENERIC) BANUFACTURERS   DOSAGE	TOTAL	ROUTE	DURATION OF	T		
(130, 632, 61)	DOSE	ROUTE (pp., im., iv. etc.)	THERAPY	DATES OF ADMINISTRATION	DISORDER	OR REASON FOR USE OF DRUG
Lincocin 8049 inj	200	im	3 da.	2/2,2/3,2/4/68		
				7-7-7-700	1 10	
	-	-				
	-	<del> </del>	-			
SUBSTANTIATING LADORATORY STUDIES (S	IND	DETAUT I	1001=4110			
SUESTANTIATING LABORATORY STUDIES (CLINICAL LABORATORY, ALTOPSY, X-RAY, ETC.)	10.11	ONTA. (I A	ODIFYING DATA			
LIST POTENTIALLY NOXIOUS OR ENVIRONMENTAL FACTORS DIPCTULE HOUSEHOLD PRODUCTS.	INDUSTRIAL	. AND AGRI	CULTURAL CHEUIC	CLINICAL LAB: DONE	ATTACHED ATTACHED	NOT DOME
EXISTING OR PALOR DISCRICERS AND PAST DRUG REACTION OR ALLERGIC HISTORY:						·
THE PART DAGG REACTION OR ALLEHOLD HISTORY:						
IF FEMAL	none	9			Pr	EVIOUS EXPOSURE TO SUSPECTED EN
CRAVITY IF PREGNA:				MAY THE SO	C	TES TO
GRAVITY PARITY				MAY THE SOUNCE OF THIS R.	PATHOLOGY	□ YES 🖄
	WEEKS OF	GESTATION				11116
DECOMPOSITION OF DRUG DINTERACTION OF TWO COLORS	WEEKS OF	E ONLY				Ø YES □ NO

NO POSTAGE NECESSARY

DRUG OUTDATED

CONTAMENATION OF DRUG

DRUG NOT USED PER LABELING
OTHER BRUG MISUSE (Specify)

DACC MISTABETED

March 11, 1968

David Rodney Davis, M.D. Roundup Montana

Lear Dr. Davis:

Thank you for taking the time to speak with me regarding your 3 or 4 patients who have experienced prolonged diarrhea following Linecoin therapy. As I understand it, these patients received only the injectable and not oral Linecoin.

Erically restating what I mentioned in our phone conversation, we have had very few reports of severe or prolonged diarrhea in association with injectable Lincocin therapy. Diarrhea, of course, has been the most common side effect with Lincocin; however, the incidence of diarrhea is tremendously lower with the injectable preparation.

Evidence to date indicates that there is no one particular treatment of Lincocin-induced diarrhea that will insure success. The enclosed abstracts offer several methods that have been used for this specific purpose. However, until the exact causative mechanism in Lincocin-diarrhea is brought to light, we cannot provide a concrete remedy.

We are, of course, continually searching for the key to the diarrhea problem. To do this we must accumulate as much information as is possible. For this reason, I am enclosing four blank Adverse Drug Effect Report forms which I would appreciate your filling out and returning.

Thank you for your cooperation in this matter.

Very truly yours,

THE UPJOHN COMPANY

Charles H. Townsend Medical Services

plo

Enclosures

MEDICINE ... DESIGNED FOR HEALTH ... PRODUCED WITH CARE Pe: Lincocin Very truly yours, THE UPJOHN COMPANY Howard H. Angell, M.D.

PJOHN COMPANY

KALAMAZOO, MICHIGAN 49001 TELEPHONE (616) 348-3571

September 13, 1956

Chie? Adverse Reaction Branch Division of Medical Information Bureau of Medicine Food and Drug Administration Washington, D. C. 20204

Reference is made to our letter of June 23, 1966, concerning a report from Dr. E. D. Fitch, Sealy-Smith Frofessional Building, 200 Horth Boulevard, Galveston, Texas, that some of his patients experienced collitia following the administration of Lincocin.

Repeated attempts to obtain further information concerning this report have been fruitless.

olg

August 25, 1965 E. D. Futch, M.D. Sealy-Smith Professional Building 200 North Bouleward Calveston, Taxas Dear Dr. Futch: · War Recent changes in the Federal Food, Drug and Cosmetic Laws require that we report promptly to the Food and Drug Administration all instances of adverse effects following the use of our preparations. We would, therefore, appreciate receiving your report concerning instances of colitis in patients on Lincocin therapy. For this reason, we are enclosing another Adverse Drug Effect Report form, which we would appreciate your filling out and returning. Thank you for your cooperation. Very truly yours, THE UPJOEN COMPANY Howard H. Angell, M.D. plo Enclosure

MEDICINE ... DESIGNED FOR HEALTH ... PRODUCED WITH CARE

### THE UPJOHN COMPANY

4114 N. CENTRAL EXPIRESSWAY DALLAS, TEXAS

June 20, 1966

TELEPHONE. Area Code 214 TAylor 4-3027

Howard H. Angell, M.D. The Upjohn Company Kalamazoo, Michigan

Dear Howard:

A Galveston internist has recently commented on the high incidence of diarrhea from the use of oral Aincocin. Proctoscopy examination of two of the diarrhea patients revealed a non-specific ulcerative colitis. The physician has reported to our salesman that in these two patients there was no evidence of fungi or ameba. The colitis disappeared within a week.

The doctor is interested in knowing if the ulcerative colitis could be due to Lincocin therapy, and he would like very much to have some word from our medical department concerning this.

Howard, we would appreciate your communicating directly with the following physician in regard to his inquiry:

> E. D. Futch, M.D. Sealy-Smith Professional Bldg. 200 Horth Blvd. dalvenion, Taken

> > Sincerely,

T. H. Tanner

rdt

interoffice memorandum

C' PES TO:

TO: File

SUBJECT: Colibin - Lincocin



FROM: H. H. Angell

DATE: January 15, 1968

As a result of information received from our Kalamazoo salesman, Mr. Fred Smith, I talked by telephone with Dr. J. William Fry of 1821 Whites Road, Kalamazoo, Michigan, concerning a patient who developed skin rash and urticaria and letter colitis following the administration of Lincocin.

The patient is a nineteen-year-old boy who was first seen by Dr. Fry on July 10, 1967, presenting symptoms of sore throat, fiver and headache along with acute nasal congestion. The boy received an injection of Lincocin 600 mg. intromuscularly and put on Achromycin and Disophrol orally. On the 25th of July, he was again seen, at which time he had arthralgia and a generalized crythema suggesting crythema multiforme and urticaria. He was treated at this time with Depo-Medrol and Benedryl.

On October 7, he developed loose stools with some blood in the stools. Since the patient had a history of amoebiasis, he was proctoscoped and ulcerated lesions of the bowel with punctate hemorrhage were found. Although no stool examinations were made, because of the history the patient was placed on antiamebic therapy. However, he grew progressively worse during the month of treatment. At this time, he was placed on Medrol Dosepak and antidiarrheal therapy and finally there was slow improvement. When the bowel was re-examined on November 30, it appeared to be normal.

It seems very probable in view of the patient's history and the nature of the lesions that this colitis was amoebic in character, even though no laboratory evidence of this was obtained.

HHA:plp

DESIGNED FOR HEALTH ... PRODUCED WITH CARE UPJOHN COMPANY KALAMAZOO, MICHIGAN 49001 TELEPHONE (616) 345-3571 January 23, 1968 Adverse Reaction Branch Division of Medical Information Bureau of Medicine Food and Drug Administration Washington, D. C. 20204 Re: Lincocin Sterile Solutions Case # 546 Commence of the second Enclosed are copies of records and reports, which are submitted in accordance with the requirements of Section 507 (g) of the Federal Food, Drug and Cosmetic Act, concerning an instance of colitis in a patient who had had Lincocin and other preparations. It will be noted that the patient had only one injection of Lincocin. In all probability, because of a history of amoebiasis and the appearance of the bowel lesions, the colitis was amoeoic in nature. Although this incident occurred several months ago, it was not brought to our attention until January 15, 1968. - 1911 T. 2414 Contract to the second second This report was submitted by Dr. J. William Fry, 1821 Whites Road, Kalamazoo, Michigan. Very truly yours, THE UPJOHN COMPANY Howard H. Angell, M.D. כוכ Enclosures



DEPARTMENT OF HEALTH, EDUCATION AND WELFARE FOOD AND DRUG ADMINISTRATION WASHINGTON, D.C. 70204	DRUG EXPERIENCE R		DUDGET GUREAU NO.
DATE SENT TO FOR BIGNTH, DAY & YEAR   MITIAL REPOR	PATIENT INITIALS AND IDENTIFICATION NUMBER		ACCUSED NO DESTROY VIE DOCUM
	BASIC REACTION DATA		
SEX HEIGHT (INCHES) NEIGHT (LOS.) DATE OF DIRT		- SHEETORY	DATE OF REACT ON CHIEF
- A. D. 1700 - 20014-	CAY TOTAL	MATERICAN COTHER	12 22 57 Married 3AV 1549
SOURCE OF REPORT IVEG., HOSPITAL, ETC.) MAME OF REPORTING P		CET, CITY, STATE, AND E CODE.	
Robert G. Collier, M.D.	307 N. Jackson Helena, Montana		
DESCRIBE SUSPECTED AGVERSE REACTION !! AND ANY POSSIBLE ASS	DETATION WITH THE DRUGIS! INVOLVED		OUTCOME OF REACTION TO DATE
Lincocin Began 12-20-67 for a wound and drained. Diarrhea began 12-23- 11-29-67 before therapy and procto	.67. Failed to respond to conserv revealed a mild proctitis. Admit	rative R. Had rects	Int, opened   ALIVE WITH SECURIAE  al bleeding   RECOVERED  5-68. Procto   STILL LANCE TEXAS.
revealed ulcerative polypoid mucos placed on steroids and azulfidine v	and bionsy showed same. Ba enem	na done - diverticul	la in sigmoin des (Gir Date et Care)
LIST ALL THERAPY IN ORDER OF SUSPICION (Manufacturer: L	st NDA or IND no.)		
NAME OF DRUGS MANUFACTURE TRADE (GENERIC) CONTROL NO.	RS DOSAGE TOTAL SCUTE CURATION OF THERAPY	DATES OF ACMINISTRATION	DISCRIBER OR REASON FOR USE OF DRUG
Lincocin	000 mg   12-20-67   qid 2 gm P0   12-28-67		Infection finger
Prednisone rapidly to 10 mg		Steroid and 1.0 on 2-21-68	
Azulfidine	2 gm giả 8 prn F0 2-12-68		Rash so DC'à
	IMPORTANT "CDIFYING DAT	TA .	
Biopsy - Ulcerated inflammed, coly	ooid mucosa	CLINICAL LAB: TO NE BIOPSY/AUTOPSY: TO NE	EATACKED ENCTIONS EATACKED ENCTIONS
None	EDUSEHOLD PRODUCTS, INCUSTRIAL AND AGRICULTURAL CHEV.	CALSI	
Existing on phica displaces and past bald headton on alle Mong however this pt. seems to me		n ulcerative soliti	s marked heartfully The The
GRAVITY PARITY	YEEKS OF SENTATION	ARMED FORCE INSTITUTE OF	FATHOLOGY: TO THE
	FOR FDA USE CHLY		FOR MEG USE CALY
MEASTIRE PACTORS NEWFOR ALL APPLICAGE TO SERVE TO BRIDE MASKY TATHERT TO CANODISASE TO CAUCA	SE DRUSS CROWN TOTAL PER LARGELY CO. S. C.	CT ORNO OUTCATES CT CONT	ASSISTANCE OF DELC

DESIGNED FOR HEALTH ... PRODUCED WITH CARE KALAMAZOO, MIC IIGAN 49001 TELEPHONE (816) 343-3371 April 25, 1968 Adverse Reaction Branch Division of Medical Information Bureau of Medicine Food and Drug Administration:
Washington, D. C., 20204 Washington, D. C. 20204 Re: Lincocin Capsules Case # 554 With reference to our letter of February 13, 1968, concerning a. report of diarrhea in association with Lincocin therapy, we are enclosing additional information. It will be noted that this patient had had evidence of proctitis with ulcerative polypoid mucosa prior to the onset or Lincocin therapy. It is extremely doubtful that Lincocin played any role in this patient's proctitis. The reporting physician also states that in his opinion the patient has personality characteristics compatible with ulcerative colitis. This report was submitted by Dr. Robert G. Collier, 307 Worth Jackson Street, Helena, Montana. Very truly yours, THE UPJOHN COMPANY Howard H. Angell, M.D. plo Enclosures

#### COLLIER

CG: Distribea

approximately one wouths and a half ago at which time the small cystic actuators was therefore by Dr. Collier from the listle flager on the right and. It is the thought to be a traffic actuator was traveled by Dr. Collier from the listle flager on the right and. It is the thought to be a traffic actuated to the discal joint at that thought. Subsequent to this patient it was uperficial wound infection and mas traded with Lincocta. The expected distribed did appear and because it was a mild cature it was ignored and the drug was contained until the finger had healed adequately. Distribed however, paraisted and became worse following the stopping of Lincocia. The patient is now having 3-10 loose success seeds par day. There is no blood in them. Only previous history of trouble was the patient approximately two to three months ago was seen by Dr. Collier in the office at which the it was noted that the patient had either vaginal or prectal bleading. The origin which was not certain. A pelvic examination did not show any abnormalities except which was not certain. A pelvic examination did not show any abnormalities except will attribute vaginitie but a proctoscopic emaination showed a rather normal sigmoid and rectum with a secure of processing which was thought to be the site of the source of

PAST WIDICAL HISTORY: Mysterectory. Allergies: none unknown.

REVIEW BY SYSTEMS: LIBERT: Negative. CARDIO RESPIRATORY: No complaint. GI: See history of present illness. GU: No vaginal bleading, discharge, dysuris or frequency.

FAYSICAL EXCHINATION: Blood pressure: 13/80. Pulse do 88 and regular. Respiration 16 per miliate. In general, the patient is an elect, competent, comewhat obese white MATTY: is accurive.

HECK: Is supple. Pulses are good.

CHAST: Clear to PSA.

MEART: Mordal sinus thytom. No purmurs. No cardiomagaly.

BREAGTS: Within normal limits.

Adomical: There is no organomegaly or henderness.

EXTRIMITIES: Within normal limits. except for nome deforalty and a lark cratic structure at the state of surgery on the right limits.

MEUROLOGICAL EXAMINATION: Is physiologic.

IMPRESSION: Ulcerative collitis, present before but aggravated by Lincocia therapy. R/O regional enteritis.

February 13, 1963

R. G. Collier, M.D.

Dear Dr. Collier.

I am writing with regard to our phone conversation of Friday, February 9, concerning the fifty-eight-year-old female patient who experienced diarrhea and colltis in association with Lincocin therapy.

As I mentioned over the phone, prior reports of rather severe diarrhes and name colitia have been received. Although we are engaged in projects designed to reveal the mechanism for this type of response, our efforts have been unsuccessful.

It is interesting to note that although sigmoidoscopic examination of the course has revealed a picture similar to ulcerative colitis, the clinical course of the process is not typical of the above disease. On the other hand, these patients have usually responded to Azulfidine and steroids when more conservative therapy was unsuccessful.

In accordance with our phone conversation, I am enclosing a blank idverse Drug Effect Report form which I would appreciate your filling out and contaming at your carliest convenience.

Thank you for your cooperation in this matter.

Very truly yours,

THE UPJOEN COMPONY

H. V. King

Incloure

117

#### CONSULTATION RECORD



11117

R.M.Count * A.Grebnell

1 .....

4. 9

Consulting Service or Physician:  Dr. D. K. Mario	For consultation only.
Report requested regarding:	For consultation and treatment.
	Signature of Attending Physician

REPOR.

This 49 year old white female fractured her right hip on August 19th. It was plated and, at the time of the operation the was started on Limitaln (I.H. for two doses and then orally for two doses in 500 mg. strength. This was followed by some leaseness of the stools but then the antibiotic was discontinued the Charden coased and she was reasonably well at the time of transfer to the Corgo Kospital.

Subscripting, housest, watery distribut with tenesing re-etarted and it became so profess that we-example to 8th Jessyh's the necessary.

Since exhibition to hospital, the diarchea has continued over the 9-day cardistion. However, her general chate appeared to be improving, particularly in relation to her state of hydratica. Showely about admission on the 27th August, the received a 2-day course of Ampicilian. Sabsequently, this was stopped. **A to no time has there been bleed noted in the etcole. Henover, her accomplished as noted to have falled if you. This to the hip-platfing to the present values of 9 to 9.6 yms. This to count has been 15,000 and 11,000. Shool cultures are reported negative on a simple coession and blood cultures also are a particular to 35 or 39 dags.

Distriction of his kery inclinion a buck of co-called shoundie force of a line by, which counts as if it were note like the character of three months requiring Corticons for his oranization. Port po it is this varient form of palendromic characters. In 19 1, the had a left breast eyet removed. Coherants, the had seen well.

Chase exclosion of hospital she has toveloped acute enthritis involving both in a and the third motocorpal-pholongeol foint hard bother cymptoms are clicited on functional inquire.

Signature of Consultant

CORSUMNATION RECORD

RM. Grant # A. Grobnoff

A ....

4. 9.69

Cosselling Service or Physician:	For consultation only.  For consultation and supportive car  For consultation and treatment.
	Signature of Attending Physician.

REPORT

MINGROM, WYDERINGTON shows a well nourished, everueight Miles famile in no distress. B.P. 120/75. Poleo &, and regular.

Head and nocks

Megabire. Optile fundi normal. No lymphedenopathy.

Thyroid not enlarged; chest elear.

Chesis: Brondics

No maccon. hung fields elear.

Yung C.V.S. Abdument

Clinically normal. Amendmention of the abdomum reveals a 4 to 6 cm. parame. No abdominal disterbion. Bowel sounds are

semantat hyperactive in muchos. No bruits are heard. Liver and oplicen are not felt. There is a vague reciptance in the R.E.Q. with clight teniernose.

Hollower, I comes definitely delineate

Rockell and polivie comminations were not done as the is to undergo a Signal consequence charthy.

Lacomotor System: Reveale both imeas are bandaged but the states that the subliming in the left impo particularly cinco ecommonda i la mon recurred. There is en combo arthrapis involving the lost third notacorpsimail my al joint.

1: 30: 000/

Newcyce have been reviewed one allow a non-epocarile colibis involving the descending colon. Where appears cles to is come non-specially occur בריים שלים כונים בונים.

that there expending has fell pathie whose discussio until to see that her frames common in. its the moment, it is now difficity a non-excellic collisis probably related to the initial use of Timescin with Por the remain, I would be freliged to many her only symptomatically SULLOSEPHIS MOSPITAL VICTORIA, S.C.

consultation record

R.W.Grant * A.Grabnoff

A	¥.	. 7	-	*1		
* ,			-	-	-	

4. 9. 69

Consulting Service or Physician:	For consultation only.
Dr.D. H.Weit	For consultation and supportive care
Report requested regarding:	For consultation and treatment.
	Signature of Attending Physician

REPORT

using Codein and Basid. The arthritis - if this is alcorative colivie is then causatively related. However, it may be an independent process such as palandropic rhounation with an acute flarcup causal by the stress of her recent illness.

Thank you for allowing no to see this patient. I will discuss her in detail with you.

RIM/pp/ d. L. 9. 69 t. 5. 9. 69

Signuture of Consultant

R. H. MIT, M.D.

EST AMA (OQ, MICHIGAN 4900) TELEPHONE (016) 382-4000

amober 21, 1959

Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Machington, D. C. 20204

Re: Lincocin Capsules & Sterile Solutions
Case # 747

conclosed are copies of records and reports which are submitted in accordance with the requirements of Section 505 (g) of the Federal Cood, Drug and Cosmetic Act; concerning an instance of diarrhea with collisis in a 49 year old female in association with Lincocin therapy.

Tits report was submitted by Dr. R. H. Wait, 204 Medical Dental Guilding, 1120 Tates Street, Victoria, B. C.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D. Chief, Drug Experience Section

Ancto ures

UPJOHN MEMORANDUM Addressed to Sales Co-ordinatogusject: -Lincocin - Colitis Coples to Date: 1st March. R.S. Haines From: Dear John, I have today seen Dr. A.N.Hill of 224, Evelyn St. S.E.S. who has disturbing reports of side effects following 3 cases developed severe diarrhoea with bloody Lincocin capsules. stools, pus and mucous on about the third day of treatment and all showed ulgeration of the newel on proctoscopy. The first patient, a girl of 20 also had a sigmoidoscopy which showed ulceration up to and beyond her diarrhoca lasting for 13weeks. Dr. Hill is in my opinion one of the most & ...etent G.P's. in S.E.London, only the fact that he has hed three such cases has led him to believe that they were not true ulcerative colitis. He has not reported these doccurrences pefore to anyone except that the first patient had to be admitted to hospital. He will provide full case histories if we would like. He still uses Sterile solution.

MEDICINE...
DESIGNED FOR HEALTH...
PRODUCED WITH CARE

# THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001 TELEPHONE (818) 345-3571

June 17, 1966

Daymond E. Barzilai, M.D. Division of New Drugs Antibiotic Drug Branch Bureau of Medicine Food and Drug Administration Mashington, D. C. 20204

Dear Doctor Barzilai:

# 320-322-330

Re: Lincocin Capsules

Unclosed are copies of records and reports, which are submitted in accordance with the requirements of Section 507 (g) of the Federal Food, Ding and Cosmetic Act, concerning three instances of diarrhea in patients receiving Lincocin.

This report was submitted by Dr. A. W. Hill, Brockley Lodge, U.E.4, London, England.

Very truly yours,

THE UPJOET COMPANY

Howard H. Angell, M.D.

11.0

Pholosures

Frontal sinusitis.  Many years frontal sinusitis and fluid levels on X-Ray and sinus punctures.  DRUGS ADMANSTERRO DURNO PRESENT HLIMES  NOH OF DRUGS DOMAGE FROM (Good Drug) TO (Good Drug)  LINCOLYCIN 500 mg. tds. 27.12265. January 1st 1966  Nil in present attack.  Diarrhoea - Gross Proctitis (8 cms)  Nil except negative stool pathology.  From Colors Proceedings of the State of Pathology.  From Colors Procedulation. Direction (170 my 200 mg.	LINCOMYCIN.		AND DATE	ADVENSE CENTRE NOTED AND DATE OF OWNER DIARTHOGIA JANUARY 4th				
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Final Outcome Still Under Observation     Permanent injury (Gree Hotors)   No Fallow-Up   Death (Give Date)   Autopyy (Give Findings)	HISTORIS OF LAUTENING TANK	Nil exce	pt negative sto	ool pathology.				
FINAL OUTCOME Shill Under Observation X No Sequelae .  [ Permandiciples (Give Bisture)		· · · · · · · ·			1			
FINAL OUTCOME Shill Under Observation X No Sequelae .  [ Permandiciples (Give Bisture)					V			
FINAL OUTCOME Shill Under Observation X No Sequelae .  [ Permandiciples (Give Bisture)					Britis en 150 De 2 mart 2 e 15 de 150 martin			
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Permanent injury (Give Nature)  No Follow-Up  Death (Give Date)  Autopsy (Give Findings)  None  Aponess								
Permanent injury (Give Nature)  No Follow-Up  Death (Give Date)  Autopsy (Give Findings)  None  Aponess	•							
Page 12 to 1	FINAL OUTCOME	Still Under Obs	ervalion	X No Seque	lae .			
Page 12 to 1	Permanent injury (Gree Nature)		No Follow-Up	Death (C	ive Date)	Autop	sy (Give Findings)	
Account 22								
Account 22				<u>-</u>	:			
Account 22		1						
	CAUG A. 1000	I'm ativense et	None .		. (			
				• .		• • • •		
	***** ** ***** ** ******** ****					. TOAL		
	A.R. HILL		Вес	ockley Lodge,	5.E.		18.3.66.	

LINCOMYCIN	AND DATE O	Diarrhoe			•
TIENT WENTIFICATION	OCCUPATION	Clerk	40	F	Márried
THEY CAME TOCATED	<u>'</u>		1		,
Frontal sir	iusitis .	<u> </u>			
		·			
2 year hist Cleared bef	tory of recurrence on inhalations	. X-Rays not done and Tetracycline	e but clini	cally he	doubt.
	DRUGS ADMINIS	TERED DURING PRESENT I			
NAME OF DRUG	DOSAGE	FROM (Give Dote)	DURATION OF AD	MINISTRATION	TO (Give Date)
LINCOMYCIN	500 mgs. t.d.s.	4.1.66.		8	.1.66.
EINCOAICIN	000851 0100				
		<del></del>	•		· · · · · · · · · · · · · · · · · · ·
		•			<u> </u>
		•			
or history by Lucing Nil in	present attack.				/
		· · · · · ·			
	•				
Diarrho	ea with blood and m	nucous	•		
Gross p	roctitis (8 cms	s.)			
ASULTS OF CARDINATIONY TESTS	G	· · · · · · · · · · · · · · · · · · ·	•		
		· · · · · ·			1.
WBCs an	d ESR Normal .				
CHICK THE COLUMN STREET	Resolved three week	ks (Kao	lin and Mor	ph.)	
	,				•
1 (-)		X No Sequelos		•	
FINAL OUTCOME SHILL	nder Observation .	•			
Permanent Injury (Give Nature)	No Fallow-Up	Death (Give De	10) .	Avio	psy (Give Findings)
	. \				
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SHUT COMISS AND TACTORS OTHER THE	Non	ne		•	
HART OF HISTORY OF STREET	AOUNESS			DATE	
		Trockley Lodge.	S.E.4.		18.3.66.

LIN	COMYCIN					cember 20th 196
TENT IDENT FICATION		OCCUPATION	Secretary	22	F	Single
Oti	tis Media	(Rt.)	sided .	•		
or PULSENT ILLNESS		Mittu Mad	in and U.R.T.I.			
Rec	urrent (Rt)	citis Med	ia and U.R.T.I.			
			DUDING BOSCENT	UINESS.		
		DRUGS ADMINI	STERED DURING PRESENT	DURATION OF	ADMINISTRATION	ı
NAME OF DRUG	DOS	SAGE	FROM (Give Date	)		TO (G Date)
Lincomycin	500 mgs		Dec. 17th 1965		D€	c. 21st 1965
						•
				<del></del>		
PROSE DISCOUNTERS N	IL					
CCINICAL MAINTENANTS D	iarrhoga with	blood an	d mucus. Procto. showed pus fill	scopy showe	ed severe	proctitis and
S	ignoidoscopy	to 15 cms	. showed pus fill	ed ulcers.		
INCLUDING ADVENSE EFFECTS A	b. 89% ·	WBC Nor	mal ESR Norma	1		
	swab for ulcer	B. Col	i and Strep. Faec	alis.		
			•			
COMP & CREEK TO LOANS DEVEL	and Grove die	arrhohea a	s above treated w	ith Knolin	and More	h. only. Oppat
		,				
				·		
FINAL GUICOME . [	X Still Under Observation		No Sequelos			
		. No Follow-Up	Death (Gire	Date)	_ Au	opsy (Give Findings)
t i comment layory (Cove Nature)				· . · · · ·		
	·		·			
		• • •	1 .	>	·	
CHUS A COME TO THE MAY CAUSE	O THIS ADVINSE EFFECTS	None -	"tendency" to ulc	erative col	litis not	excluded.
					• .	
Same of members, marriage		Austre			DATE	18.3.66.
A.N. 1	III.		Brockley Lodge, S	.E.G.	. 220.0 5.42 5.22	U. 1

YERS: DRU	G EFFECT REPORT		THE UPJOHN COMPAN	
i Januari	AG. C. C.	(PLEASE TYPE OR PRI	KALAMAZOO, MICHIGA	Ņ
	in sure in the		SEAT MANTEN STATES	
	·			
. 1	over 50 patie	nts so far) have	had some form of	
	from 3-4 days or	loose stools to	almost prostration fro	ora
	terrinea. There have	been no deaths b	at I know of two local	
	mother EWT man's) w	ho had colld uggl.	utinins found while	
	DRUGS ADMINISTERE	D DURING PRESENT ILLN		
NAME OF THE PARTY OF	DOSACE	DURATION OF	ADMINISTRATION TO (Give Date)	
united i eli	for ulcerative (?) co	litis which did	not respond even when	
re Arm. Chia	conycia) was withdraw	n.		
		•••		
		· · · · · · · · · · · · · · · · · · ·	<b></b>	
			LOT NUMBER OF DIRES UPO	
	· · · · · · · · · · · · · · · · · · ·	· · · · · · · · · · · · · · · · · · ·		
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,				
AM. Catti (m.	STATE UNDER OBSERVATION	LING SEQUELAS	***	
	KO TOTLOW UP	( DEATH (Give Dire)	[ ] AUTOPSY (Give Findings)	
		•		· · ·

h18 E. Lancaster, Mayne, Pa.

MALAMAZOO, MICHIGAN

January 12, 1966

Raymond E. Barzilei, M.D. Division of New Drugs Antibiotic Drug Branch Bureau of Medicine Food and Drug Administration Washington, D. C. 20204

Dear Doctor Barzilai:

Re: Lincocin, Capsules and Sterile Solutions

In accordance with the requirements of Section 507 (g) of the Federal Food, Drug and Cosmetic Act, we are advising you that we have received information from Dr. E. L. McKenna, 418 East Lancaster, Mayne, Pennsylvania, that he has encountered some degree of "diarrhea" in approximately 50 percent of the patients he has treated with Lincoein. This, of course, is for in excess of the percentage seen by other clinicians.

We have not been able to obtain individual case reports from this physician.

Very truly yours,

THE UPJOIN COMPANY

Howard H. Angell, M.D.

plp

Enclosure

Linuocia	2	. Ulcerative coli	tis 3.	Diarrhea	1-1-66
THE TELEPHONEATION	oc oc	Housewife	58	F	M ·
Di-M. K.					San E days but t
cook it 4 days. I					
lays. Before end			iarrhea	and sev	ere pruritus
enus acea 5" in di		oriation, etc.	ILLNESS		
	T			MINISTRAT	TION
NAME OF DRUG	DOSAGE	FROM (Gi. + Date)		T	O (Give Date)
Lincocin	500_mg.	Dec. 28, 1965 about Jan. 2 c			1, 1966 then 1966
Preatment - Mycos	tatin 500 mg.	orally gid			
Bacid Tablets ora					
Consitive to tetr					
and some other fo					2007314469
and some other to					
at manufestations are constructed prunity	s - Sigmoido:	scopy exam showed	a swoll	Len rect	al and sigmoid
rucosa with much					
1-11-66 and 3-8-6					
diverticulitis wi					
mulignency nor ul	cerative les	ions noted. No d	ilatati	on of co	lon or abnormali
in contraction.	Very slow cl	earing of the col	onic an	d mucosa	and the blood
rucous. The prux	itus cleared	and recurred aft		ing at f	irst nearly
PERMANENT HUDBY (GIV. N	utura) [] NO FOLI	LOW-UP (3 DEATH (	Give Dore)	[] AUTOF	PSY (Give Findings)
Still under obse	ervation.		. —		
est history".	Last office watch. Sorr much milder		- pruri itus an	tus fine	clly cleared.
Stanley H. Brown,		ODAL M. MCNTCHOTE	, 1(d • 1)€	C. O. C. I	10-29-00

PLAINTIFF'S EXHIBIT A 46-LL NO. KELSHIK

KALAMAZOO, MICHIGAN 49001 TELEPHONE (616) 345-3571

November 10, 1966

Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

\$ 313

Re: Lincocin Capsules

With reference to our letter of June 14, 1966, concerning an instance of diarrhea in a patient on Lincocin therapy, we are enclosing additional information received from the physician.

This report was submitted by Dr. S. H. Brown, 8544 West McNichols, Detroit, Michigan.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.

2010

Enclosures

Sale Service Control

HALAMAZOO, MICHIGAN

March 24, 1967

Chier
Aiverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

#384

Re: Lincocin Capsules

Reference is made to our letter of December 28, 1966, concerning a report of diarrhea in association with Lincocin therapy. Since our initial letter to you, we have received further information concerning this report which we are enclosing.

This report was submitted by Dr. D. B. Cameron, 3503 Perry Street, Mount Rainier, Maryland.

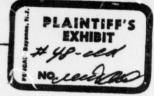
Very truly yours,

THE UPJOHN COMPANY.

Howard H. Angell, M.D.

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inc Losiuros



			1 1	1
. WAS DOSE RED	DUCED?	)		No received
If reduced,	dosage Disco	ontinued comple	tely	· . ·
Did side eff	fect disap ear a	fter reduction? (		
	•		·	
	SCONTINUED? (	) Yes		
If discontin	nued, did side e	ffict disappear? (	Yes Yes (	) No
If yes, was	drug reintroduc	eed?		No No .
If yes, did	side effect rea	appear?	) Yes (	) No
<del></del>	···	<del></del>		
What other measures, i	if any, were eff	Sective in control	ling side effe	ct(s)?
At the sign of dia After henorrhage & every 3 hours. Ri	& intolerable heo-Macrodex.	tenesmis Sedo	corticos	porine I.M.
Approximate number of	patients treate	ed by you with this	drug.	
Approximate number of Very few - 2 or		ed by you with this	drug.	
	This patienty. The wound das an emerge At that time the sippy. #2 description of the second action - hemonometric in the second action - hemonometric in the second in the	nt left the hos healed by prigency for giant he was taking liet for the trond admission hearthagic coliti	pital on the mary intent urticaria an antichol eatment of a stopped a	ion. He and edema energic his duodenal ll'medication
Additional comments:  post-operative day was rehospitalized of the glottis. and an antacid with ulcer. Three days  First allergic rea Second reaction -	This patienty. The wound do as an emergent that time the sippy. #2 do section - hemogiant urtical	nt left the hos healed by prigency for giant he was taking liet for the trond admission herrhagic colitional.	pital on the mary intent urticaria an antichol eatment of stopped a	ion. He and edema energic his ducdenal
Additional comments:  post-operative day was rehospitalized of the glottis. and an antacid with ulcer. Three days	This patienty. The wound do as an emergent that time the sippy. #2 do section - hemogiant urtical	nt left the hos healed by prigency for giant he was taking liet for the trond admission herrhagic colitional.	pital on the mary intent urticaria an antichol eatment of a stopped a	ion. He and edema energic his ducdenal
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Additional comments:  post-operative day was rehospitalized of the glottis. and an antacid with ulcer. Three days  First allergic rea Second reaction -	This patien y. The wound d as an emerg At that time th sippy. #2 d s before secon action - hemo giant urtical	nt left the hos healed by prigency for giant he was taking liet for the trond admission herrhagic colitional.	pital on the mary intent urticaria an antichol eatment of stopped a	ion. He and edema energic his duodenal ll' medication
Additional comments:  post-operative day was rehospitalized of the glottis. and an antacid with ulcer. Three days  First allergic reasecond reaction -	This patienty. The wound does an emergant that time the sippy. #2 does before second action - hemogrant urtical factors.	nt left the hos I healed by prigency for giant he was taking liet for the trond admission herrhagic colitionia.	pital on the mary intent urticaria an antichol eatment of stopped a	ion. He and edema energic his duodenal ll' medication
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Additional comments:  post-operative day was rehospitalized of the glottis. and an antacid with ulcer. Three days  First allergic rease Second reaction -	This patienty. The wound does an emergant that time the sippy. #2 does before second action - hemogrant urtical for the signal of the signal o	nt left the hos I healed by prigency for giant he was taking liet for the trond admission herrhagic colitionia.	pital on the mary intent urticaria an antichol eatment of stopped a	ion. He and edema energic his duodenal ll' medication

Lignature of Reporting Physician:

"Laurent Michaud, M.D."

### SIDE EFFECT REPORT

# THE UPJOHN COMPANY OF CANADA

Name of Upjohn Drug: Lincocin
Name of Reporting Physician: Dr. Laurent Michaud
Address: 565 Commerciale St., La Tuque, Quebec
Patient's Identification (Initials Only)
Patient's Age: 24 Sex M Height 6'2" Weight 210
Primary Diagnosis: Pilonidal fistula
Pertinent History: History of duodenal ulcer without complication
for several years. Purulent recurrent discharge arising from a coccygoal abscess for several months.
Duration of illness: Specific Indication for which drug was used:
Several months Purulent discharge arising from the coccygeal region.
Concomitant therapy:
Mylonta (Parke Davis) - 1 tablet with Lincocin per os.
Describe side effect or side effect complex:  Hyperpensials is Collowed in a few hours by Crequent diarrhoea with Liquid stools. Finally rectal tenesmis, intestinal cramps, melena, intestinal hemorrhage, state of profound shock.
How long ondrug when side effect appeared? How long did side effect last? 72 hours
Lincocin 500 mg. d.i.d. x 3 days - 27-30 November / Lincocin 500 mg. g. Lincocin 500 mg. b.i.d. x 2 days Nov.30-Dec.1 /x 48 hrs. Dec.2 & 3
Date Drug Stopped Initial dosage Nov.28-30 incl. Nov.30-'Dec.2 I.M Evening of Dec. 3
Dosage when side Dose Frequency Rouse effect appeared:
500 mg. q.i.d. per os for 36 hrs

MEDICINE...
DESIGNED FOR HEALTH...
PRODUCED WITH CARE

# THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

February 16, 1967

MEDICAL SERVICES
Office of
HOWARD H. ANGELL, M.D.

Chief
Adverse Reaction Branci
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

Re: Lincocin Capsules

Enclosed are copies of records and reports, which are submitted in accordance with the requirements of Section 50% (g) of he Federal Food, Drug and Cosmetic Act, concerning a patient ho developed diarrhea and urticaria following the administrat on of Lincocin.

This report was submitted by Dr. Laurent Michaud, 565 Commerciale Street, In Tuque, Quebec.

Very truly yours,

THE BEJOHN COMPANY

About A II. Ancell, M.D.

1.11.

Enclosures

NEGELPT NORTH TOTAL

FEB 2 3 1957

Feed and Targ Libraries at Best And Head and Targ Libraries, & Welfare

मा स्थाप प्रदास्था है।		(PLEASE TYPE OR PRINT)	THE UPWAN COMPANY	
* Y 3	ADVENS	E-FECT NOTES		
Lincocin	X GUPA F	Black stools and pu	rulent colitis	
$\circ$	01	1 Production 52	M M	
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. Improved again of	n higher dose of	Sulfathaliding.		
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a comment	· [Ad mile			
C. J. Committee,	Jr., M.D. 1116	5 Joth Ave., Sidney,	Neb. 1 3-6-66	

KALAMAZOO, MICHIGAN March 22, 1966

Paymond E. Parzilai, M.D. Division of New Drugs Antibiotic Drug Branch Bureau of Medicine Food and Drug Administration. Washington, D. C. 20204

Dear Doctor Barzilai:

= 258

Re: Lincocin, Capsules

Enclosed are copies of records and reports, which are submitted in accordance with the requirements of Section 507 (5) of the Rederal Food, Drug and Cosmetic Act, concerning an instance of protracted diarrhea following the administration of Lincocin coally.

This report was submitted by Dr. C. J. Cornelius, Jr., 1116 19th Avenue, Sidney, Mebraska.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.

Unclosures

Lincocia			AND DATE O	P ONSET Dia	rrhea				
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R. H. Golder,	M. D.		Sidne	y, New York			6	-28-65	

## THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

July 7, 1965

Reyroud E. Bermilei, M. D. Division of New Drugs Antibiotic Drug Brench Dureau of Medicine Food and Drug Administration Machington, D. C. 20204

Dear Doctor Barmilal:

Re: Zamessin, Capatles

Enclosed one copies of records and reports, which are stimulated in occordance with the requirements of faction 507 (g) of the rederal Rood, Drug and Cos stile Rot, assessmeltly as instructs of persistint distribution in a petitod who had been on bineceda therapy.

This report was sabmitted by R. H. Colder, M. D., Sidney, New York.

Very tradi, yours, and verous consists

roomed Ti. Angehit, M. D.

Thelosures

MEDICINE...
DESIGNED FOR HEALTH...
PRODUCED WITH CARE

# THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

April 11, 1966



Daymond E. Barzilai, M.D.
Division of New Drugs
Antibiotic Drug Branch
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

Dear Doctor Barzilai:

# 269

Ra: Lincocin, Cansules

Enclosed are copies of records and reports, which are submitted to accordance with the requirements of Section 507 (g) of the Federal Food, Drug and Cosmetic Act, concerning two cases of severe diarrhea occurring in patients receiving Lincocin and Lincocin plus Bicillin.

This report was submitted by Dr. Frederick S. Caldwell, 50 West Edmonston Drive, Rockville, Maryland.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.

plp

Enclosures

Lineogie.	Å.	O DATE OF ONS	diarrhea (			AMAZOO, MICHIGAN
Contraction of the		Salesman	William Sherman	40	M .	Married
oute follicular	· tonsillitis d	lue to St	rep.			
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ed Boin Onear t	Tayer, chills, sore t	hroat, swollen g	lands. (2-18-66)
	52007 JOHNS 15050	NORMA DARRENT HAND	
		DURING PRESENT ILLN	ADMINISTRATION
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lowly improving	g ns of 3-31-66		
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enderter s. C.	Harell, M.D. Rockyl	He, Miry and 20	3-31-66

and the second s

# THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001 TELEPHONE (616) 345-3571

Hovember 22, 1968



Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

Re: Lincocin Case # 625

With reference to our letter of October 24, 1968, concerning an instance of bloody diarrhea in association with Lincocin, we are enclosing additional information.

This report was submitted by Daniel Parr, M.D., Tremont, Illinois.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D. Chief, Drug Experience Section

bkp

Enclosures

October 22, 1968

Daniel Parr, M.D.

Tramont, Illinois

Dear Dr. Parre

I appractated having had the opportunity of discussing with you your observations concerning a partient who developed bloody diarrhea and colitis following eight days of oral Lincocin therapy.

In response to your request I will summerize the main points covered in prior reports of this nature.

There were two instances where microscopic characterization was included with the colids report. The first was summarized as "a severe acute inflammatory reaction involving principally the outer one-half of the mucosa." In the second report the findings were characterized as "subscure non-specific prectitie."

As I rentioned on the phone, signoidoscopic examinations have been variously described as

- 1) acute colitis:
- 2) acutely inflamed bowel without ulceration or bleeding
- 3) red, friable and granular appearing bowel
- 4) circular lesions, slightly elevated and rismed by erythema.
- 5) patches of purulent exudate with shallow ulcars beneath.

Purulence and/or exudation has not been prevalent in these reports. The reporting physicians have frequently commented that the gross appearance of the bovel resembles ulcerative colitis but is still unlike anything the, have encountered before.

The therapy employed in these instances has consisted of

- 2) antispasmoules .
- 3) azulfidine
- 4) adsorbents
- 5) occasional mention of systemic corticostoroids or steroid enemas.

Patient response to this type of management has been generally satisfactory though sometimes slow - 3 weeks to 2 or 3 months.

The mechanism by which this type of inflammatory reaction is elicited is unknown. We feel at this time that alteration of feeal flora is not responsible. Occasional instances of delayed onset suggesting possible hypersensitivity response have been reported. The intervening period between cessation of drug and onset has varied from three days to two transactions.

A final and likely possibility is a direct irritant affect by the antibiotic or one of its breakdown products. Forty to forty-five percent of the drug can be recovered in the stool following oral administration of recommended doses.

We are most interested in, and would appreciate receiving, further documentation of this experience. For this reason, I am enclosing a blank Adverse Brug Effect Report Form which we would appreciate your complaining and returning at your earliest convenience.

Very truly yours,

THE UPJOIN COMPANY

L. V. King Medical Services

2003

November 13, 1968 Daniel Parr, M.D. Tremont Tilinois, 3 Dear Dr. Parri We regret the necessity of troubling your again regarding your report or bloody diarrhea and colitis in association with Lincocin. It is not our intention to be overly persistent as we realize the heavy. burden of paper work that other types of documentation have imposed. We are, however, very much interested in obtaining all clinical information associated with the use of Lincocin. In addition, federal law and regulations of the Food and Drug Administration have made it obligatory for the manufacturers to follow up all reports of suspected adverse effects in association with their products. The enclosed Adverse Drug Effect Report form is relatively brief and may be completed from the patient's record in a short time. SERVE HOLL Very truly yours, THE UPJOHN COMPANY Howard H. Angell, M.D. Chief, Drug Experience Section Enclosure

# THIS FLAP IS GUMMED, READY TO SEAL NO ENVELOPE NECESSARY, FOLD AND SEAL NO POSTAGE NECESSARY

DEPARTMENT OF HEALTH, EDUCATION AND WELFAR FOOD AND DEUG ADMINISTRATION WASHINGTON, D.C. 20204	Ē	DI	RUG E	XPER	IENCE RE	PORT	05-094 11/67	FORM APPROVED DUDGET DUREAU NO.
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D. L. Parr, M.D.	AC OF REPORTING PHYSICIAN IS	CP HORAL!		9	nt, Illino			
DESCRICE SUSPECTED ADVENCE REACTIONIS! AND		H THE DRU	esis) invec	VED				OUTCOME OF REACTION TO DATE  ALIVE WITH SEQUELAE  RECOVERED  STILL UNDER TREATMENT  DIED (Give Date and Cause)
YOUR OPINION: DRUG RELATION								
LIST ALL THERAPY IN GROER OF SUSPICIO	MANUFACTURERS  CONTROL NO.	D no.]  DOSAGE FORM (tab, cap, etc.)	TOTAL	ROUTE (co. in., iv. etc.)	DURATION OF THERAPY	DATES OF ACMINISTRATION		DISORDER OR REASON FOR USE OF DRUG
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Howard H. Angell

MEMO

FROM Clyde R. Howse

D.O. D.O.

March 7, 1969

COPIES TO

On Wednesday evening, March 5, 1969. I conversed with D. E. Marsico, D.O. of 2900 Highland Avenue, Broomal, Pa. by phone. experienced diarrhea with large volumes of mucous material approximately one week after having received Lincocin 500 mg capsules qid for 3 1/2 pathogenic organisms. Sigmoidicance is stool cultures revealed no

pathogenic organisms. Sigmoidioscopic examination revealed a colitis-like condition. There was no ulceration present, and only a slight amount of blood was observed with the initial evacuation of mucous material, and none subsequently. has been treated with Lactinex, Azulfidine, systemic corticosteroids and Medrol Enpak. At this time, has improved a 1639, which he assured me he would complete and return.

PLAINTIFF'S EXHIBIT

April 30, 1969 D. E. Marsico, D.O. 2900 Highland Avenue Broomal, Pennsylvania Dear Dr. Marsico: I am writing with regard to my letter of April 14, 1969, requesting brief information concerning your report of colitis in association with Lincocin therapy. The state of the s .If at all possible, we would appreciate receiving the completed Adversa Drug Effect Report form which I enclosed. For your convenience, I am enclosing another form. As I mentioned before, we are very much interested in obtaining all clinical information associated with the use of Lincocin. Further, federal law and regulations of the Food and Drug Administration have made it obligatory for the manufacturers to follow up all reports of suspected adverse drug effects in association with their products. Thank you for your cooperation in this matter. Very truly yours, The state of the THE UPJOHN COMPANY

Howard H. Angell, M.D. Chief, Drug Experience Section

bkp

Enclosure

### THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001 TELEPHONE (616) 343-3571

May 9, 1969

Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

Re: Lincocin Capsules
Case # 668

With reference to our letter of March 7, 1969, concerning an instance of colltis in association with Lincocin therapy, we are enclosing additional information received from the reporting physician.

This report was submitted by D. E. Marsico, D.O., 2900 Highland Avenue, Broomal, Pennsylvania.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D. Chief, Drug Experience Section

bko

Enclosures

Branch - 3 Phil. March 7, 1969 D. E. Marsico, D.O. 2900 Highland Avenue Broomal, Pennsylvania 19008 Dear Dr. Marsico: I appreciate having the opportunity of discussing with you your boservation who developed diarrhea and colitis following three and one-half days of oral Lincocin therapy. "concerning The second secon As I mentioned on the phone, therapy employed in the few instances reported in the past has considted of A STEEL PROPERTY. 1) low residue diet 2) antispasmodics 3) azulfidine
4) adsorbants
5) occasionally, systemic corticosteroids or steroid enemas. Patient response to this type of management has been generally satisfactory though sometimes slow - 3 weeks to 2 or 3 months. I am enclosing the Adverse Drug Effect Report form which I mentioned on the phone, and would appreciate your completing and returning it to me. We are highly interested in obtaining all information available on incidents of this. nature and will welcome any material you are able to provide. THE REPORT OF THE PROPERTY OF Thank you, Dr. Marsico, for informing us of this condition, and your interest in The Upjohn Company. Sincerely. J. 4. 4. 18 37. 1 THE UPJOHN COMPANY Clyde R. Howse Medical Services bkp Enclosure

A.3	TADVE E FFE	PLEASE TYPE	OR PRINTI		KALAMAZOO, MICHIGAI
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OF POSSIST ILLA					
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r_Diarrhea c	ontrol				
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G ADVINE ELECTS					
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ST ICE WITH CATTLE		OCCUPATION DIGITIES	AGE	SEA	MARITAL STATUS
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ay be to the first of					•
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netteociti, devi	eloped vaginit		Mr. M. C. C.		··
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J. C. Brenema	1	Galesburg, Michi	gan	5/	15/67

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### THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

May 24, 1967

462/

Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

#462

Re: <u>Lincocin Capsules and</u>: Sterile Solutions

Enclosed are copies of records and reports, which are submitted in accordance with the requirements of Section 507 (g) of the Federal Food, Drug and Cosmetic Act, concerning two instances of diarrhea in patients treated with Lincocin.

These reports were submitted by Dr. J. C. Breneman, Galesburg, Michigan.

Very truly yours,

THE UPJOHN COMPANY

Howard R. Angell, M.D.

plo

Enclosures

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promotional material accompanying the companys drug Lincours. how, I don't like taking a drug that comes to me under these Conditions. Since it appraised have been used as a part of your researche, I expect to be compensated for the ill health it has coured me. Since it has her our 1/2 years since I took Lineven, and I am still unable to form a solid stool and have a lot of rectal travelle resulting from the dearrica caused they Lincoline. The Mucaus Carletis has shown no emprecement. as I statel in my first letter - if you are interested in making an out of Court settlement with me, let me know.

JUN 30 1969 MED SERVICES June 25, 1969. The Uppalme o. Kalamagao, mucheyani. mr. L. V. King Dear Sin: I am a little late in answing your letter, as I was out of town Eichen et arrived. I am sending you the named of the physicians wells prescribely the antihestic, Lincoun, also treated, and deagnosed. I know doctors are very reluctant to almit anything that would huit their reputation and turing, and will do everything to protect themselves and earlither. Since my lyperience with Lincoin, I have learned a great

PECEIVED

deal about doctors and drugs. I have read heaps and writings by well-known altorneys and others which has enlightened me about -doctors and drugs, and drug companys. also all the ham that can he - Caused the patients. This prominent attorney also says there are doctors who have the courage to admit the truth about harm caused to -patients. I have hefore me an article uchich appeared in the Julia prehune about two weeks ago which says, "The upform lo. enclosed "5 checks With materials seit to doctors that promoted the firms product Senator Goyland nolson addel" think it raises a number of ethecal questions. Nelson produced a Copy of

Physicians: Dr. Orcilles M. Rippy 1603 whith. Prescribel & treated & Stillwater Oka, On Lon & Fred 810 Stellusta, Okla, diagnocal. Stellusta, Okla, nucus Cailetes. Dr. Paul J. Reynolds 5205-5-Penn.
diagnosed and Oklahoma City, Okla. Sincerely,

Juna 12, 1969

I am writing with regard to my letter of May 29, 1969, requesting the

we have a continuing research interest in learning all we can about our products and, therefore, the problem you present in association with Lincocin is of interest and importance to us.

The second of th We are enclosing a self-addressed stamped envelope for your convenience. in giving us your physicians name and address.

Thank you for your cooperation in this matter. Very truly you THE UPJOHN COM

Very cruly yours,

THE UPJOHN THE UPJOHN COMPANY

L. V. King Medical Services

Enclosure

MEDICINE ... DESIGNED FOR HEAL PRODUCED WITH CARE

# PJOHN COMPANY

KALAMAZOO, MICHIGAN 49001 TELEPHONE (616) 345-3571

August 15, 1969

Adverse Reaction Branch Division of Medical Information Bureau of Medicine Food and Drug Administration Washington, D. C. 20204.

Re: Lincocin Capsules

Case # 702

With reference to our preliminary report of May 29, 1969, concerning an instance of diarrhea and colitis in association with Lincocin therapy; we are enclosing additional information received from the reporting physicians,

This report was originally sent in under the patient's name.

the reporting physicians were Orville M. Rippy, M.D., 1603 W. Ninth, Stillwater, Oklahoma; Leon C. Freed, M.D. 810 S. Vealaut, Stillwater, Oklahoma; and Dr. Paul J. Reynolds, 5205 S. Penn, Oklahoma City,

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D. Chief, Drug, Emperience Section

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Enclosures

# THIS FLAP IS GURRED, READY TO SEAL

NO ENVELOPE NECESSARY, FOLD AND SEAL NO POSTAGE NECESSARY

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TO THE	ARMED FORCE INSTITUTE OF PATHOLOGY	-		2000		
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DISORDER OR REASON FOR USE OF DRUG	DATES OF ACMINISTRATION .	DURATION OF THERMPY	DOTAL ROUTE	teh, cen, etc.)	S MANUFACTURERS CONTROL NO.	TRADE (GENERIC)
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REACTION FACTORS ICHECK ALL APPLICABLE DOXES!

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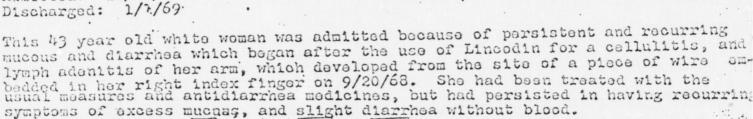
CO SONS CASO SONS CASO SONS CASO CO

□ BENE COLLEGIED -

CO CONTAMUNATION OF DAUG

MISSISSIPPI BAPTIST HOSPITAL
DISCHARGE SUMMARY

Admitted: 12/26/68 Discharged: 1/7/69



Physical examination revealed no significant findings.

Laboratory studies: Admission hemoglobin 14.2, hematocrit 43 percent, WBC 10,300 with a normal differential. No EOS noted, sed rate 18 mm. per hour. Admission urinalysis had a specific gravity of 1.020, which no albumin, sugar, or pus. Her stools were negative for occult blood, ova, cysta, and parasites on three occasions. Stool examination showed a moderate yeast. VDRL was nonreactive. Serum bilirubin .45 with .1 direct. BUN 14. mg. percent, calcium 9.5 mg. percent, phosphorus 3.0 mg. percent, chloride 107, cholesterol 211 mg., CO2 28.2 mg. percent, potassium 4.0 M/cq. Control protein 7.3 grams percent, with 4.1 albumin. Serum sodium 140 M/cq per liter, fasting blood Sagar 92 mg. No pathogenic organisms were isolated from stool cultures. T-3 30.2.

She had an abebrile course in the hospital. Her stools contained excess mucus, but there was no diarrhea. Her cholecystogram was normal. Upper GI and small bounds studies were completely negative. The lumbar spine showed disc disease with secondary arthritis of the lower lumbar spine. An IVP was normal. The color study showed normal filling without evidence of spasm or polyps or other disorder. Electrocardiogram was within normal limits. Sigmoidoscopic showed normal mucchs membrane to 18 cm.

It is my continued feeling that the persistent mucous colitis is the residual of the Lincocin treatment which canadaproctitis as well as vaginitis. She should make an uneventful recovery in time.

She is discharged to continue Mierostatin by mouth, along with butter milk and Cantil with each meal.

Prognosis is good.

Benjamin P. Folk, Jr., M.D.

BPF:mle

### UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001 TELEPHONE (616) 345-3571

November 24, 1969

Chief White Adverse Reaction Branch Division of Medical Information

Bureau of Medicine

Food and Drug Administration

Washington D. C. 2022 Washington, D. C. 20204

Re: Lincocia Capsules Case 7 734

With reference to our preliminary report of September 26, 1969, concerning an instance of stomatitis and gastroenteritis in association with Lincocin therapy, enclosed is additional information. 

This report was originally submitted by the patient;

However, the physician involved was Benjamin P. Folk, Jr., M.D., 615 Medical Arts Bldg., Jackson, Mississippi.

Very truly yours, min r

THE UPJOEN COMPANY -

Howard H. Angell, M.D. Chief, Drug Experience Section

Enclosures

102 dameo Place Colonia, H. J. April 1, 1966

RECEIVED

APR 8 1966

MED. SERVICES

Val Christenson
The Upjohn Co.
hO Seventh Ave., Co.
Hew York, N. Y.

Dear Val,

According to the company's request I am reporting some sovere reations to Lincocin with the names and addresses of the physicians involved.

Louis Gianvito, M. D., 666 Castleton Ave, Staten Island, NY
3 cases of colitis, possibly ulcerative
Ludwig Gross, M. D., 915 Jewett Av. Staten Island, NY
Colitis 1 or 2 patients

Luis Moreno, M. D. 2580 Amboy Rd. Staten Island NY 2 cases of Giant Urticaria (I already reported these two to Kalamazoo)

C. Mantell, M. P., 86 Hamilton Av. Staten Island, NY (Gastroenterologist)

l or 2 cases of colitis

M. Frew, M. D. 791 Jewett Av., Staten Island, NY Diarrhea caused by the injectable Lincocin.

Albert S. Angrisani

### THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

June 14, 1966

Paymond E. Barzilai, M.D. Division of New Drugs Antibiotic Drug Branch Dureau of Medicine Food and Drug Administration Washington, D. C. 20204

Dear Doctor Bargilai:

#306

Pa: Lincocin, Carsules and Sterile Solutions

Teference is made to our latter of April 13, 1966, concerning a report of colitis in association with Lincocin therapy.

Repeated efforts to obtain further information from the reporting physician, Dr. Louis Gianvito, 665 Castleton Avenue, Staten Island, New York, have been fruitless.

Very trule yours,

THE UPJOHN COMPANY

Howard H. 'Angell, M.J.

n7.n

ADVERSE DRUG EFFECT REPORT THE UPJOHN COMPANY (PLEASE TYPE OR PRINT) KALAMAZOO, MICHIGAN ADVERT ETTECT HOTEL KANE OF UNIONA DAUG 15 days diarrhea Lincocin OCCUPATION MARITAL ATATUS MATIENT IDENTIFICATION Surgeon CONDITION BEING THEATED Sinusitis MISTORY OF PRISENT ILLMESS Pains maxillary area. DRUGS ADMINISTERED DURING PRESENT ILLNESS DURATION OF ADRINISTRATION DOSAGE HAME OF DRUG FROM (Give Dete) 500 mg. q. 6 h. Lincocin LOT NUMBER OF DRUG USED PART METUNY INCLUSING This form intrigues me .. Three patients the usual dosage of In approx. 2-3 days developed severe abdominal cramps, severe dierrhea with blood. Perienal slight nausea, Stool cultures, two of these normal. fissures. in this matter, you could solve this without extended form to fill CLIMENT COUNTY FOLLOWING DEVELOPMENT HO SEQUELAE FINAL OUTCOME STILL UNDER OBSERVATION AUTOPSY (Give Findinge) HO FOLLOW-UP DEATH (Give Date) PERMANENT INJURY (Give Hetere) To Up ohn Company. HI YOUR DENIEN, WHAT FACTORS OTHER THAN EMELIFIC DRUG ACTION, COULD HAVE CAUSED THE ADVENCE EFFECTS אוסוויאי ביודי פיודים 91519th Street, Washington, D, C.

MEDICAL SERVICES

MEDICINE...
DESIGNED FOR HEALTH...
PRODUCED WITH CARE

### THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

April 5, 1966

Raymond E. Berzilai, M.D.
Division of New Drugs
Antibiotic Drug Branch
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

Dear Doctor Barzilai:

Re: Idncocin, Capsules

Enclosed are copies of records and reports, which are submitted in accordance with the requirements of Section 507 (g) of the Federal Food, Drug and Cosmetic Act, concerning four instances of diarrhea following the administration of Mancocin.

This report was submitted by Etreet, Washington, D. C.

915 19th

Very truly yours,

Hoyard H. Angell, H.D.

gig

Enclosures '

THIS FLAP IS GUMMED, READY TO SEAL

NO ENVELOPE NECESSARY, FOLD AND SEAL

NO POSTAGE NECESSARY

DEPARTMENT OF HEALTH, EDUCATION AND WEL FOOD AND DRUS ADMINISTRATI WASHINGTON, D.C. 20204	FARE				IENCE RE	PORT	95-1	505 505	APPROVED NO		•
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y H. Kwak, M.D. (as	transcribed by T	he Upjoh	n Co.)	Ha	vre-de-Gr	ace Clinic,	608 So:	ath Union,	Havre-de	-Grace, Md.	
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	ERACTION OF TWO OR MORE DRUCS ERDOSAGE DRUG MISLAGE			ISED PER LAS MISUSE (Spec		D DRUG OUTDATED	CONT.	AMENATION OF DRUG			-

MEDICINE ... DESIGNED FOR HEALTH ... PRODUCED WITH CARE KALAMAZOO, MICHIGAN 49001 TELEPHONE (616) 345-3571 MEDICAL SERVICES Office of HOWARD H. ANGELL, M.D. December 2, 1969 Chief Adverse Reaction Branch Division of Medical Information Bureau of Medicine Wood and Drug Administration Washington, D. C. 20204 Re: Lincocin Capsules Case # 731 reference to our preliminary report of September 25, 1969, concerning an instance of colitis in association with Lincocin therapy, repeated strempts to obtain additional information from the reporting physician have proven fruitless. This report was submitted by H. H. Kwak, M.D., Havre-de-Grace Clinic, 608 South Union, Havre-de-Grace, Maryland. Very truly yours, THE UPJOHN COMPANY Chief, Drug Experience Section oko inclosures

Liverpool, n. 4 Lincolin mal 3/2/2 & dianher: 1 à colitie Robert Walker ma 101 2nd lot QU 315 457-3570 1-5 daily Jhur 1693:45 If going to have signoidizeope and shyring will let us know that with in about a we

MEDICINE...
DESIGNED FOR HEALTH...
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#### THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001 TELEPHONE (616) 345-3571 Nay 22, 1269

Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Gashington, D. C. 120204

Re: Lincocin Capsules ... Case # 687

With reference to our letter of April 9, 1969, concerning an instance of colitis-type reaction in association with Lincocin therapy, the physician stated that the patient was going to hawasigmoidiscope; however, repeated attempts to obtain this information from the reporting physician have proven fruitless.

This report was submitted by Robert Walker, M.D., 101 2nd Street, Liverpool, New York.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D. Chief, Drug Experience Section

bin

Paclosures

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eround the anus.	The drug was d	iscontinued but t	he intermi	ttont diar	rhes conti
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		ct revealed 2-3 m		losions,	
had disappeare	d by repeat pr	ctoscopy 10 Nov.	O&P and	e iristorm	ure negati
JAICAE COURS FOLLOWING DEVEL	OPMENT	proved within two			
and did not rec	ur.				
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PERMANENT INJURY (GIVE	Nature) No FOLLO	DEATH (GI	ve Date)	AUTOPSY (Give Fi	nding•)
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ACTION, COULD HAVE CAUSED	only an undiag	mosed condition,	perhaps id	liopethic c	olitis
It is peculiar t	hat theeffoct	of the drug (if i	t was the	drug) uns	so long.
were resustant estimat When G. Willia		USAD The Pentagor	Washinton	14 Nov	rember 196

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MEDICINE...
DESIGNED FOR HEALTH...
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## THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001 TELEPHONE (616) 345-3571

. Movember 28, 1966

Chief Adverse Reaction Branch Division of Medical Information Dureau of Medicine Food and Drug Administration Washington, D. C. 20204

半373

Re: Linguin Cansules

With reference to our letter of Movember 2, 1966, concerning diarrhea in a patient on Lincocin therapy, we are enclosing additional information.

This report was submitted by Captain Edward Williams, US Army Dispensary, Pentagon, Washington, D. C.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D.

212

Inclosures

Red. 26. 1966 The liggodes Company Coil Place, L. h.y. ilentlemen ; I feel it is my duty to inform gen of the friling events which have transpired as a limit of taking sie Djour medications. There is no question in my mind as to the name and reputation of your good Company. Lowever the latter is written for the pumpose of possibly available a similar situation toppening

to someone clas and for white On actober 1= 1966, I vivited my physician with a piece chest ered; which was alragnose as tronchitis the prescribed dincrein Capsuler, 500 mg, for relief of their condition; (one: capitale there times a day, to be. taken one and on half there before meals). This medication was taken for thee days and on October 4th I became viry ill with a painful. gaster intestinal distinbance resulting in severe diariles. This condition became progressively worse, developing

unto a extito. I have been under the continued care of my physician since which has his abstituted my taking additional costly medication as Well are repeated visite to his office. I am the mother of two pomell children and I feel that my lose of Leath has impaired not buty my Velface but also that of my children Sow the passe thee weeks they have tun deprived of my pervices pince atill mit over the effects of their illness. Her may verify the above

facto with my physician.

dr. Joseph Pedulla, n. d.

242 haples Senace

Brong, Den York # 1046 I expect, upon in nevering the alone, I will be hearing from you. · Very Souly Joune : (mus.)

MEDICINE...
DESIGNED FOR HEALTH...
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#### THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001 TELEPHONE (613) 382-4000

October 21, 1969



Chief
Adverse Reaction Branch
Division of Medical Information
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

Re: Lincocin Capsules
Case # 748

Enclosed are copies of records and reports which are submitted in accordance with the requirements of Section 505 (g) of the Federal Food, Drug and Cosmetic Act, concerning an instance of diarrhea with colitis in a 70 year old male in association with Lincocin therapy.

This report was submitted by Dr. R. H. Wait, 204 Medical Dental Bldg., 1120 Yates Street, Victoria, B. C.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M.D. Chief, Drug Experience Section

Enclosures

any at the refer to the security to store item. the contract the best one the least to the terminal and the least and a laccol values were notational.

September 3, 1969

. . The tes that Mr. into had a postentiblete contents. tes the stampinescopy of a moderatory exets and cortice. Dr. D. Longridge, brings up the possibility that this, in fact, in late 1029 Douglas Street, els or some sora smaille colleis, sister accuelei Victoria, B.C.

-! have accounted for a colon reway, steel as overes block communities ifficiently so distinct or money the Dear Doctor Longridge:

was seen on September 2, 1969, and I thank you for this referral. He states that he was perfectly well until approx. 4 weeks ago, when he developed an infection involving the lateral aspect of the left index finger. This was incided and subsequently he received a 4 or 5 day course of an antibiotic, which I presume to be Lincocin. Toward the termination of this course of therapy, he noted some change in the stool frequency and within a few days he had watery digrehea which has persisted since then. Currently he has between 4 and 6 movements pur day, chiefly at night, associated with urgency, tenesmus and meteorism. At no time has he observed blood in his stools. There is associated anorexia and nausea, with a 6 lb. weight loss during the 3-week period.

Prior to the onset of this illness he had no complaints referrable to his g.i. tract and his previous medical history is completely unremarkable except for 'flu in 1918.

The family history reveals that both parents died of arteriosclerotic heart disease. There is no diabetes or Tb. in the family.

Functional enquiry is by and large negative. Personal habits include the former consumption of 20 digarattes per day, but for the last 3 months ha has ceased smoking. He drinks approx. one quart of milk per day and uses 2-3 cups of tea or coffee. He is on no other medications. There is no recent history of foreign travel, although he visited Scandinavia one year ago and Mexico 2 years ago.

Physical examination revealed a well-nourished, remarkably well-preserved male appearing younger than his stated age of 70 years. The B.P. was 130/82 in the right arm, sitting, the pulse was 84 and regular. Examination of the heed and neck revealed a small amount of wax in the right ear canal, bilateral arcus senilus and complete dentures. There was no lymphadenopathy. Thyroid was not enlarged. The trachea was central. Lung fields were clear. C.V.S. was clinically normal and the paripheral pulses were intact. Exemination of the abdomen revealed mild general tenderness, no distention, . average bowel sounds and no bruits. Liver and spleen were not felt and there was no tenderness to fist percussion. Rectal exemination revealed a flat small prostate and a minimal degree of anal sphincteric spasm. Locomotor system was unremarkable. Deep tendom maflexes were physiological, plantars downgoing.

Richard H. Wait

own/inte

Dr. D. Longridge,
1029 Dougles Street,
Victoria, B.C.

Re:

Dear Doctor Longridge:

\[
\text{was seen again on September 3, 1969, following completion}
\]

was seen again on September 8, 1969, following completion of investigation. He states that at the present time there has been progressive improvement of the diarrhea so that he is now having only 2-3 soft movements per day and there has been no bleeding per rectum. The barium colon x-ray is reported as normal; however, upon review of these films I feel that there is definite evidence of mucosal irregularities extending at least to the transverse colon from the sigmoid. The remainder of the investigation including billrubin, alkaline phosphatase, CSC and urinalysis, can be considered to be within normal limits. Sedimentation rate is slightly elevated at 29 mm/hour.

A rectal blopsy which was performed at the time of the initial visit shows unusual numbers of plasma cells and polymorphonuclear cells, which is part of a non-specific interstitial inflammatory infiltration.

As appears to be progressively improving spontaneously, except for the ingestion of yogurt, I feel that the diagnosis of postentibiotic diarrhea is the most likely explanation for his recent problem. However, as I explained to him, the possibility of ideopathic ulcerative colitis cannot be excluded at this time. I would suggest that a repeat sigmoidoscopy be done in 10 days time to check regarding his improvement and if the mucosa appears to be normal than the antibiotic diarrhea would be more or less confirmed.

Thank you again for allowing me to evaluate his case. I should be pleased to check him once again should you so desire.

Yours sincerely,

Richard W. Wait

RHW/mls

MEDICINE... DESIGNED FOR HEALTH... PRODUCED WITH CARE

TELEPHONE

RECEIVED

## THE UPJOHN COMPANY

3730 EAST 48TH AVENUE DENVER, COLORADO

March 19, 1965

J. A. Hall, M.D. Medical Research - General The Upjohn Company Kalamazoo, Michigan

Dear Dr. Hall:

We would like to report another Lincocin reaction. Lyle F. Haberland, M.D., 595 Avenue B, Powell, Wyoming, telephone 754-4262, treated a patient with the "flu,"

| He prescribed one capsule four times a day.

She developed severe diarrhea and her son, who is a pharmacist, suggested she stop the drug. Fifteen hours later, the physician again started her at four capsules a day. At the end of another day and a half of therapy, the diarrhea returned and she had some swelling and puffiness around the eyes.

The patient also developed considerable sinus drainage. Shortly thereafter, she was hospitalized with colitis. She reported that she had had no sinus problems previously. Insofar as I know, she had received no other medication than Lincocin Capsules.

Will you please contact Dr. Haberland about this apparent reaction.

I would like to say that I received the Interoffice Memorandum from Dr. Angell to you reporting a hypotensive reaction to Lincocin therapy. This is the first report we have had of this nature, and I would like to say that it is excellent in that it gives a complete record for our files about this type of reaction.

I hope that this system of reporting will be continued.

Yours very truly,

THE UPJOHN COMPANY

George H. Forney

GIE : cmk

#### THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

May 14, 1965

Raymond E. Berzilai, M. D.
Division of New Drugs
Antibiotic Drug Branch
Bureau of Medicine
Food and Drug Administration
Washington, D. C. 20204

Dear Doctor Barzilai:

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Re: Lincocia, Capsules

In accordance with the requirements of Section 507 (g) of the Federal Food, Drug and Cosmetic Act, we are advising you that we have received a report that Lyle F. Haberland, M. D., 595 Avenue B, Powell, Wyoming, had encountered an instance of diarrhea and edema of the face in a patient following the administration of Lincocin Capsules. We understand that the patient had had a course of therapy of approximately three days at the time this occurred.

Repeated efforts to obtain further information have been fruitless.

Very truly yours,

THE UPJOHN COMPANY

Howard H. Angell, M. D.

olg

# TELETYPEWRITER MESSAGE

DEPT. 312

JUN 3 1985

LI 20

ATT MEDICAL SERVICES

0

DR. S. KURZWEIL, 3599 EASTCHESTER ROAD, BRONX, N. Y. PLACED
MALE PATIENT ON LINCOCIN CAPSULES. PATIENT TOOK 9 CAPSULES OVER 3
DAYS, DEVELOPED ACUTE DIARRHEA WHICH HAS DEVELOPED INTO COLITIS.
PATIENT NOW UNCOER CARE OF AN UNKNOWN GASTRO ENTEROLIGIST WHO
ATTRIBUTES PROBLEM TO LINCOCIN. PATIENT IS THREATENING DR. KURZWEIL
WITH LEGAL SUIT.

J T SISELE SALES CONTACTOR



MEDICINE...
DESIGNED FOR HEALTH...
PRODUCED WITH CARE

upjohn

### THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

July 30, 1965

Raymond E. Barzilai, M. D. Division of New Drugs Antibiotic Drug Branch Bureau of Medicine Food and Drug Alministration Washington, D. C. 20204

Dear Doctor Barzilai:

4/37

Re: Lincocia, Capsules

In accordance with the requirements of Section 507 (g) of the Federal Food, Drug and Cosmetic Act, we are advising you that we have received a report that S. Kurzweil, M. D., 3699 Bastchester Rock, Arona, New York, has encountered a patient who developed severe diarrhea following the administration of nine Lincockn Capsules in a period of three days.

Repeated attempts to obtain further information have been fruitless.

Very truly yours,
THE UPJOHN COMPANY

Howard H. Angell, M. D.

olo

